For Hemophilia A patients,

YOU USE YOUR JOINTS MORE THAN YOU THINK.

That’s why you need a Factor VIII treatment you can Count On to protect you and your joints from bleeds.

ELOCTATE® (Antihemophilic Factor [Recombinant], Fc Fusion Protein) is an injectable medicine that is used to help control and prevent bleeding in people with Hemophilia A (congenital Factor VIII deficiency). Your healthcare provider may give you ELOCTATE when you have surgery.

IMPORTANT SAFETY INFORMATION

Do not use ELOCTATE if you have had an allergic reaction to it in the past.

Tell your healthcare provider if you have or have had any medical problems, take any medicines, including prescription and non-prescription medicines, supplements, or herbal medicines, have any allergies, are breastfeeding, are pregnant or planning to become pregnant, or have been told you have inhibitors (antibodies) to Factor VIII.

Allergic reactions may occur with ELOCTATE. Call your healthcare provider or get emergency treatment right away if you have any of the following symptoms: difficulty breathing, chest tightness, swelling of the face, rash, or hives.

Your body can also make antibodies called “inhibitors” against ELOCTATE, which may stop ELOCTATE from working properly.

Additional common side effects of ELOCTATE are headache, rash, joint pain, muscle pain and general discomfort.

If you have risk factors for developing abnormal blood clots in your body, such as an indwelling venous catheter, treatment with Factor VIII may increase this risk.

These are not all the possible side effects of ELOCTATE. Talk to your healthcare provider right away about any side effect that bothers you or that does not go away, or if bleeding is not controlled after using ELOCTATE.

SEE PLEASE BRIEF SUMMARY OF PRESCRIBING INFORMATION ON THE PREVIOUS PAGE

YOU HAVE QUESTIONS. CoRes HAVE ANSWERS.

Dedicated Cores are passionate about helping people in the Hemophilia community.

Understanding Cores are advocates with decades of experience who understand the community’s needs.

Accessible Cores prioritize face-to-face conversations to get to know you. They’re just a call, text, or email away.

Sanofi

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**esperoct**
antihemophilic factor (recombinant), glycopegylated-exeli

**Brief Summary information about esperoct (antihemophilic factor [recombinant], glycopegylated-exeli)**

This information is not comprehensive.

- **Talk to your healthcare provider or pharmacist**
- **Visit www.now.com/esperoct/pdf to obtain FDA-approved product labeling**
- **Call 1-800-727-6550**

**Patient Information**

**esperoct** (antihemophilic factor [recombinant], glycopegylated-exeli)

**Read the Patient Information and the Instructions For Use that come with esperoct before you start taking this medicine and each time you get a refill. There may be new information.**

This Patient Information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have questions about esperoct after reading this information, ask your healthcare provider.

**What is the most important information I need to know about esperoct?**

Do not attempt to do an infusion yourself unless you have been taught how by your healthcare provider or hemophilia treatment center.

- You must carefully follow your healthcare provider’s instructions on dose and schedule for infusing esperoct® so that your treatment will work best.

**What is esperoct®?**

**esperoct®** is an injectable medicine used to replace antihemophilic factor VIII. It is used to treat hemophilia A and is given as an infusion into a vein.

- **Please do not use esperoct® without consulting your healthcare provider.**
- **If you have any further questions on the use of this product, ask your healthcare provider.**

**What I take to see too much esperoct®?**

Alcohol

**What should I tell my healthcare provider before using esperoct®?**

- Before taking esperoct®
- If you have or have had any medical conditions, take any medicines, including non-prescription medicines and dietary supplements, are nursing, pregnant or planning to become pregnant, or have been told that you have inhibitors to Factor VIII
- If you have a family member with hemophilia

**What are the possible side effects of esperoct®?**

**Common Side effects include:**
- Rash or itching
- Swelling, pain, rash or redness at the location of infusion

**Other Possible Side Effects:**

- You could have an allergic reaction to factor VIII proteins. Call your healthcare provider right away or get emergency treatment right away if you get any signs of an allergic reaction, such as: hives, chest tightness, wheezing, difficulty breathing, and/or swelling of the face.

**When should I tell my healthcare provider before the infusion?**

- If you have or have had any medical conditions
- If you are allergic to any of the ingredients of esperoct®
- If you are allergic to hamster proteins

**How should I use esperoct®?**

**Treatment with esperoct® should be started by a healthcare provider who is experienced in the care of patients with hemophilia A.**

You may infuse ESPEROCT® at a hemophilia treatment center, at your healthcare provider’s office or in your home. You should be trained on how to do infusions by your hemophilia treatment center or healthcare provider. Many people with hemophilia A have to infuse the medicine by themselves or with the help of a family member.

Your healthcare provider will tell you how much ESPEROCT® to use based on your weight, the severity of your hemophilia A, and where you are bleeding. Your dose will be calculated in international units (IU).

- **Call your healthcare provider right away if your bleeding does not stop after taking esperoct®.**
- **If your bleeding is not adequately controlled, it could be due to the development of Factor VIII inhibitors.**

You might need a higher dose of esperoct® or even a different product to control bleeding. Do not increase the total dose of esperoct® to control your bleeding without consulting your healthcare provider.

**Use in children**

esperoct® can be used in children. Your healthcare provider will decide the dose of esperoct® you will receive.

If you forget to use esperoct®

- Do not attempt to do an infusion. Infuse the missed dose when you discover the mistake. Do not infuse a double dose to make up for a forgotten dose. Proceed with the next infusion as scheduled and continue as advised by your healthcare provider.

- **If you stop using esperoct®,**

You should tell your healthcare provider if you:

- Have been told that you have inhibitors to Factor VIII.
- Have been told you have antibodies called “inhibitors” against esperoct®, which may stop esperoct® from working properly.

**For information about ESPEROCT® contact:**

- **For Patent Information, refer to:** http://novonordisk-us.com/products/product-patents.html

**Additional Information**

**FOR ADULTS and ADOLESCENTS**

**Switching made easy**

- **With a standard 50 IU/kg dose every 4 days**
- **-50% fewer infusions if you previously infused every other day**
- **-40% fewer infusions if you previously infused 3x a week**

**Safety Proven across 5 studies, the largest and longest EHL clinical trial program**

- **Of 1% through factor levels for standard half-life (SHL) products in adults and adolescents.**
- **Compared with SHL products.**
- **Data shown are from a study where 175 previously treated adolescents and adults received routine prophylaxis with Esperoct® 50 IU/kg every 4 days.**
- **Pre-dose factor activity (trough) levels were evaluated at follow-up visits. Mean trough levels for adolescents (12–18 years) were 2.7 IU/dL.**

**esperoct®** can be used in children. Your healthcare provider will decide the dose of esperoct® you will receive.

- **If you forget to use esperoct®,**
- **Do not attempt to do an infusion.**
- **If you are allergic to hamster proteins**
- **Common side effects of esperoct® include rash or itching,**
- **Steady-state FVIII activity levels were estimated in 143 adults and adolescents using pharmacokinetic modeling.**
- **Important Safety Information**
- **Who should not use esperoct®?**
- **You should not use esperoct® if you are allergic to Factor VIII**

**IMPORTANT SAFETY INFORMATION**

- **What is esperoct®?**
- **esperoct®** (antihemophilic factor [recombinant], glycopegylated-exeli)
- **Can you use esperoct® if you are allergic to Factor VIII?**
- **If you are allergic to hamster proteins**
- **If you have been told that you have inhibitors to Factor VIII.**

**What are the possible side effects of esperoct®?**

- **Common Side effects include:**
- **Rash or itching**
- **Swelling, pain, rash or redness at the location of infusion**

**How should I use esperoct®?**

**Treatment with esperoct® should be started by a healthcare provider who is experienced in the care of patients with hemophilia A.**

**esperoct®** is given as an infusion into the vein.

**For up to 3 months.**

**For information about ESPEROCT® contact:**

- **For Patent Information, refer to:** http://novonordisk-us.com/products/product-patents.html

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**For up to 3 months.**
In this special product guide, you will find detailed charts listing all the current products and emerging therapies. You will also find important educational articles about the promise of gene therapy, the future of prophylactic factor infusions, how clinical trials work, the drug approval process, how informed consent works and the drug recall process.

The information printed in Dateline Federation is provided for general purpose use. HFA does not give medical advice or engage in the practice of medicine and recommends that you consult with your physician or local treatment center before beginning any form of treatment.

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Washington, DC 20002
202.675.6984
info@hemophiliafed.org

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Connect with us on social media for daily posts and updates about what’s happening at HFA.

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**EXECUTIVE CORNER**

**HI FRIENDS,**

HFA has long been committed to bringing you and your families the resources, tools and education you need to make informed decisions about bleeding disorders. This annual special edition of Dateline Federation is one of those valuable resources. We hope you find this tool helpful as you navigate treatment options and emerging therapies and that it might serve as a conversation starter for you and your medical providers.

I didn’t get diagnosed with von Willebrand disease (VWD) until my teenage years during an unexpected emergency surgery. After receiving my bleeding disorder diagnosis, like many of you can probably relate, it answered so many lingering questions I had, like why I was always getting bruises, had dangerously heavy menstrual periods, etc. But it was also a hard transition for me and my family. My mom had undiagnosed VWD, and one of my sisters was diagnosed as well. Thankfully, I got connected with the community through the Bleeding Disorder Foundation of Washington, which is my proud home and local member organization. I am so grateful for all the opportunities to learn, grow and lead with the incredible programming and investment of the HFA programs and my local member organization.

I got involved more directly with HFA after being asked to be a board member in 2017. It has been so fun to get to know more of the national community and connect with individuals and families from all across the country.

The programming and education that HFA offers provides me with confidence and hope as I’m now entering into conversations about how my bleeding disorder impacts my future family. HFA is so much more than an organization for people with bleeding disorders. It is for me, as a woman, future mom and community member, a place of family and community strength that offers hope, assistance, educational tools and advocacy to everyone.

**The Latest Products and Treatments**

As people with bleeding disorders and parents of children with bleeding disorders, it’s important we stay updated on the latest products and treatments available, that we learn how to speak up and advocate for our families and that we continue to empower ourselves and our community about bleeding disorders.

HFA is right there with you. This organization that I love—and have been involved with for several years—is committed to providing you with the most updated information available. HFA is also committed to continuing to ensure a safe blood supply and providing transparency around treatment options.

In this special product guide, you will find detailed charts listing all the current products and emerging therapies. You will also find important educational articles about the promise of gene therapy, the future of prophylactic factor infusions, how clinical trials work, the drug approval process, how informed consent works and the drug recall process.

We hope you find these articles valuable and consider this guide an ongoing resource to pull off your shelf (or read online at www.hemophiliafed.org/home/news-stories/dateline) whenever you have questions. And, of course, the HFA team is always available to answer your questions as well.

Let us know how we can help—or what tools and resources you’d like to see in the future. Email info@hemophiliafed.org. We’d love to hear from you!

Allie Ritcey
Chair, HFA Board of Directors
Informed Consent: A Process, Not Just a Form

BY HFA STAFF

Patients with bleeding disorders are no strangers to engaging in conversations with medical, research and pharmaceutical staff. Emergency rooms, doctors’ offices, pharmaceutical company offices, conference rooms and exhibit halls have all become places to engage in medical discussions. Each of these venues has different, but similar, codes of ethics to follow when engaging in conversations about patients’ health, and all require obtaining informed consent before conducting health care intervention or research through a study or trial. Consent can only be obtained from a mentally competent adult or a legally authorized representative of a mentally incompetent adult. This legal status refers to the capacity of a person to act on their own behalf and their ability to understand the information presented, to appreciate the consequences of acting or not acting on that information, and to make a choice.

Participation by Minors
A parent or legal guardian provides consent for a minor. However, children 12 and older who are asked to participate in a research project must do so voluntarily and must verbally assent to the research project. The explanation of the project and the language used must be appropriate to the child. In some localities, even children as young as seven are asked to assent to participate in research studies.

FDA Regulations
Under the U.S. Food and Drug Administration regulations, an Institutional Review Board (IRB) is an administrative body that has been formally designated to review and monitor biomedical research involving human subjects. The IRB has the authority to approve, require modifications needed to secure approval, or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects. (The local IRB that approves the study can provide more information about consent as it relates to children.)

Research and Clinical Trials
Consent works differently in a hospital setting versus a research/clinical trial setting. In the research/clinical trial setting, the first step to understanding is discovering that a research study or clinical trial exists. Patients may learn about the existence of a research project or clinical trial via mail, telephone, through a friend or during an in-person visit with a doctor.

Tips for Understanding Clinical Trials & Research Studies

WHAT SHOULD I ASK?

- Is a written copy of the research procedures available?
- What are the benefits and risks of this research project?
- How will I be informed if there are changes to this project?
- Am I waiving any of my rights by signing this consent form?
- May I ask a person I trust to read this document?
- Will my name and address be kept confidential or will it be shared with others?
- How will my information be stored to protect my privacy?
- May I refuse to participate in this research project?
- What if I change my mind after I agree to participate?
- How do I withdraw my consent after I sign the form?
- If I withdraw my consent and stop participating, what will happen with the information already collected from me?
- Are there negative consequences if I withdraw my consent?
- (In case of pharmaceutical trials) Will I be given the actual medication or a placebo?
- (If English is not your first language) Is the information available in my preferred language?

WHAT HAVE I LEARNED?

- The purpose of the research.
- The name, address and phone number of the principal investigator, known as a PI.
- How long I am expected to participate.
- If any of the medications or procedures are experimental.
- The possible risks or discomforts.
- If there are any alternative procedures or courses of treatment.
- If my information and medical records will be kept confidential.
- If I will be paid for my participation.
- The medical treatments available if I get injured.
- Who I can call if I have questions.
- If I am required to participate in this study.
- If there is a penalty if I refuse to participate.
- If there is a penalty if I stop participating at any time.

MORE THAN A SIGNATURE: Informed consent is about your understanding and willingness to participate in a study, not about signing a form.
A Look at the Drug Recall Process

BY HFA STAFF

It's important in the bleeding disorders community to be aware of recalls and what a recall means. It is important to pay attention when a product is recalled, but with all the different sources of information and the different types of recalls, it can be confusing. Recalls, designed to protect the public’s health, are used as a way to deliver information to consumers in an expeditious manner.

A recall is an action taken by a manufacturer to remove a product (food, drugs, medical devices and cosmetics) from the market, initiated either by the manufacturer or by request from the U.S. Food and Drug Administration (FDA). In either case, the manufacturer removes or corrects a product that is in the market and in violation of FDA rules and regulations. In both cases, the FDA considers the recall to be manufacturer initiated.

Alternatively, an FDA-mandated recall, also known as a mandatory recall, occurs when FDA orders a manufacturer to recall a product or mandates recall requirements. The FDA’s role is to oversee the manufacturer’s recall strategy, monitor the recall for effectiveness and classify the recall.

### RECALL CLASSIFICATION

**Class I:** Includes a health hazard situation in which there is reasonable probability that the use of the product will lead to serious, adverse health consequences or death.

**Class II:** Includes a potential health hazard situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

**Class III:** Includes a situation in which use of or exposure to the product is not likely to cause adverse health consequences.

**Market withdrawal:** When a product has a minor violation that would not be subject to FDA legal action a “market withdrawal” occurs. The product is removed by the firm from the market or the firm corrects the violation.

**Medical device safety alert:** Released in circumstances in which a medical device may present an unreasonable risk of substantial harm. These situations also are considered recalls in certain cases.

Each FDA recall follows specific timelines and procedures depending upon the circumstances. For example, each recall is initiated with a written order that states the violation, the product, lot and serial numbers to be recalled, and the timeline for the recall. Each recall is unique and requires its own recall strategy developed by the Center Recall Unit (CRU). The CRU will consider how far the recall should extend; whether the public needs to be warned and, if so, in what geographical area; and the appropriate assessment for recall effectiveness. A recall designated voluntary, requested and mandatory depends on who initiates the process. Based upon the gravity of the situation, the FDA will issue a public warning.

### RECALL METHODS

#### Voluntary Recall: Initiation of a Recall by a Manufacturer

Consistent with its responsibility to protect the public health from products that are defective or potentially harmful, a manufacturer may voluntarily initiate a recall. If a recall is manufacturer-initiated, the FDA reviews the information provided by the manufacturer, conducts a health hazard evaluation, classifies the recall and then advises the manufacturer in writing of the assigned recall classification. The FDA then places the notice of the recall in the FDA Weekly Enforcement Report. Nearly all recalls implemented in the U.S. are begun on a voluntary basis by the manufacturer.

If a manufacturer has voluntarily initiated a recall, it is the manufacturer’s responsibility to promptly notify each of its direct accounts. If the recall extends beyond direct accounts, then the direct accounts should be instructed by the recalling manufacturer to contact sub-accounts that may have received the product. Once all the accounts have been informed about the recall, they must promptly follow the recall strategy that was previously put in place for that account.

#### FDA Requested Recall

In urgent situations, the FDA may request a recall. The request is directed to the manufacturer that has the primary responsibility for making or marketing the product. Class 1 category recalls are the most often requested recalls. It is important to note FDA considers an FDA-requested recall to be manufacturer initiated.

The associate commissioner for regulatory affairs approves all recall requests from FDA. A letter outlining the need for a recall is sent to the manufacturer. After a recall has begun, the recall is entered in the Recall Enterprise System, which is a database used by the FDA to submit, update, classify and terminate recalls.

#### FDA-Mandated Recalls

The FDA’s authority to issue a mandatory recall is very limited. Subjects of mandatory recalls can include devices, biological products, human tissue intended for transplantation, infant formula, tobacco products and food. The FDA also has discretion to order a mandatory recall if it finds that a human cell, tissue or cellular or tissue-based product is a source of dangerous infection to humans or does not adequately protect against communicable disease.
OUR VISION: A WORLD WHERE NO LIFE IS LIMITED BY GENETIC DISEASE

At Spark® Therapeutics, we are committed to discovering, developing and delivering gene therapies.

We believe investigational gene therapy has the potential to be transformative in the treatment of hemophilia and we understand the importance of developing gene therapies that meet the needs of the hemophilia community. Our priority is the safety and well-being of clinical trial participants.

EXPLORE THE SCIENCE OF GENE THERAPY RESEARCH

Be informed and feel empowered when you learn about the field of gene therapy and its potential application for hemophilia.

Learn about gene therapy research for hemophilia.

Discover what gene therapy is meant to do.

See a demo about the science of gene therapy.

Explore frequently asked questions about hemophilia gene therapy clinical trials.

Interested in enrolling in a Spark-sponsored hemophilia gene therapy clinical trial?

Want to know more about gene therapy clinical trials?

Visit HemophiliaForward.com
Imagine a day when you or someone you love no longer needs to spend time each week getting prophylactic treatment for a bleeding disorder. Gone is the time spent driving to a treatment center. Gone is the need to sit through scheduled time-consuming intravenous (IV) factor infusions. Gone, too, is the fear of repeated bleeds and their long-term health impacts.

This is the potential of gene therapy. And while this potential has yet to be fully realized, experts in bleeding disorders treatment say an approved gene therapy is well within our grasp.

“Gene therapy has the potential to make a huge difference,” said David Clark, PhD, chair of the Coalition for Hemophilia B. Clark is a retired pharmaceutical scientist who helped develop plasma and recombinant factor VIII (FVIII) and factor IX (FIX) products.

What we know—and don’t know—about emerging gene therapies

BY DARA CHADWICK, FREELANCE WRITER
“Gene therapy has the potential to make a huge difference.” However, “we don’t really know yet whether we can call it a cure.”

—David Clark, PhD

The idea of injecting a virus into your body may sound scary. But adeno-associated viruses can’t make you sick. “They’re not active viruses anymore, and they don’t have any genes that necate to them active viruses,” Pipe said.

AAV vectors are coated with a specific protein that encases the gene that produces FVIII or FIX (think of the gene as being wrapped in a package). Once the AAV particles reach the liver, the protein coat interacts with certain receptors on the surface of the liver. The receptors tell the liver to accept the AAV, allowing the genes to reach the nucleus inside each liver cell. Once there, liver cells help the genes to express and begin producing FVIII or FIX.

“We put specific elements alongside the FVIII and FIX gene so that it will only be expressed in the tissue that we want it to—in this case, the liver,” Pipe said. “These liver-specific genetic elements are called promoters and enhancers. That way, even if the gene did get into non-liver cells, the gene would not express because the ‘machinery’ in the cell would not recognize it.”

It’s important to note that gene transfer, or gene therapy that delivers a working gene to help the body produce FVIII or FIX, doesn’t affect how bleeding disorders may be passed to a person’s offspring. “Patients will still be able to transmit hemophilia to their children,” Clark said. Some researchers are trying to develop gene therapies that don’t use viruses to deliver the gene, according to Clark. “Some companies are using nanoparticles, which are small particles made of fats or lipids,” he said.

Pipe highlighted three achievements for gene therapy: “We have well-established treatments and protocols using factor-replacement therapy and now Hemlibra that are affording unprecedented bleed control and convenience for patients and allowing them to live their lives to potential,” Pipe said. “With that backdrop, what is gene therapy looking to achieve?”

Pope highlighted three achievements he hopes gene therapy will deliver: sustained full restoration of blood coagulation, a way to deliver long-term effective treatment without the need for frequent infusions, and an acceptable ratio of treatment safety to effectiveness.

“Ideally, we want a genetic therapy that is not going to have unacceptable toxicities or significant risks over the long term,” Pope said. “And the last overarching aspiration for gene therapy is we want to be able to offer this to as many patients as possible. The reality is none of the genetic therapies to date meet all the check boxes for our aspirations yet. But that’s course for optimism that the current wave of therapies is really going to offer something worth considering if they get approved by the regulators.”

Sonji Wilkes, vice president of public affairs for HFA, shares that optimism about gene therapy’s potential: “We don’t do this method of...
“Anything that can safely and effectively make a positive difference is a good thing. Our job is to help people understand what the risks and benefits are. Some people are going to be early adopters and some aren’t.”

—Sonji Wilkes

gene therapy in young children with hemophilia,” he said. “This platform of therapy likely will not result in long-term expression in a young child because the liver is actively growing.”

Also potentially excluded are people who produce certain antibodies that may make gene therapies ineffective. “The human immune system is pretty smart, and it has a long memory,” Pipe said. “We all get exposed to natural adeno-associated viruses in the community over the course of our lives, beginning in early childhood.”

These viruses don’t cause disease, but our immune system sees them and produces antibodies against them. “Unfortunately, we’ve found that as many as 50% of the patients we screen for clinical gene therapy are not eligible because of these cross-reacting antibodies,” Pipe said. “When someone is interested in gene therapy, the first thing we do is test them for these neutralizing antibodies.”

Another concern is that in some people, the infused gene therapy may trigger an immune reaction—their body sees the AAV carrying the gene as a threat and releases immune cells to fight it. An immune reaction can require some people to take potent corticosteroids (such as prednisolone) to suppress this immune response.

“Eventually, these AAV protein elements are cleared and there’s no more immune response,” Pipe said. “You’re able to come off the immune-suppressive therapy. Hopefully, on the other side of that, you end up with a sustained expression of your FVIII or FIX.”

Unanswered Questions

With all its potential, unanswered questions remain around gene therapies for people with bleeding disorders. Will gene therapy treatments produce consistent levels of factor in every person? Will the therapy’s benefits eventually wear off? And if they do, can the same person be treated with gene therapy again?

“Different patients end up with different results,” Clark said. “A big thing with gene therapy is it seems it’s not always reproducible. There’s a lot of things in hemophilia that we don’t really understand, including exactly what determines how people bleed. That’s one of the problems with gene therapy. We’re showing that it works, but there’s still a lot of unknowns.”

The potential for gene therapy access issues raises even more unanswered questions, according to Wilkes. Will those who meet eligibility criteria be able to get gene therapy near them? “A good majority of bleeding disorder patients get their treatment from a federally funded hemophilia treatment center,” she said. “It’s pretty reasonable to think that not all of those are going to offer gene therapy. You might not be able to drive 30 minutes down the road to get treatment. It might be the next state over.”

Also unanswered is the question of payment for costly gene therapy treatments. “We know already that payers are slow adopters to any new drug a lot of times,” Wilkes said. “We don’t know the cost and whether payers are going to be willing to pay for it. There’s a lot of questions about how the payment model is going to be set up to pay for this. And I don’t think any of us have figured that out yet. We’re at the mercy of how payers end up deciding how to do this.”

Pipe agreed that there are some important unknowns around gene therapy. “Are we going to get a good enough outcome for these patients for them to embrace some uncertainty with what levels they’re going to achieve, whether they’re going to get a good response and how long it’s going to last?” he said, noting that some people might also be concerned about potential unknown adverse events.

Still, for eligible patients, gene therapy offers the promise of producing enough of their own factor to avoid the need for prophylactic therapy. “They can live their lives,” Pipe said. “It’s a one-time treatment that could potentially last a decade or more.”

Takeda is here to support you throughout your journey and help you embrace life’s possibilities. Our focus on factor treatments and educational programs, and our dedication to the bleeding disorders community, remain unchanged. And our commitment to patients, inspired by our vision for a bleed-free world is stronger than ever.
EVERY STEP HAS BEEN EVOLVING
THE SCIENCE OF GENE THERAPY IN HEMOPHILIA B

1970
First patients ever receive gene therapy

1997
First rFIX products approved by FDA

1999
First gene therapy trial in hem B

2018
Late-stage trials for gene therapy in hem B underway

We’re working to make gene therapy a reality for you.

Explore the advancing science behind gene therapy at HemEvolution.com
Using factor as a prophylactic treatment to ward off bleeds has become a regular part of the lives of people with bleeding disorders. However, advances in medical technology offer hope for products and therapies that might reduce or eliminate the need for frequent infusions. In fact, some already exist, but many more are in the clinical trial pipeline. But what does that mean for factor products? How relevant will standard and extended half-life factor be in light of the ongoing development of new products, including gene therapy?

Many experts don’t think that advances such as gene therapy will eliminate the role of factor and factor products—at least not any time soon.

“I think factor is going to be around for quite a while, let me just say that,” said David Clark, PhD, chair of the Coalition for Hemophilia B. Clark is a retired pharmaceutical scientist who helped develop plasma and recombinant factor VIII and factor IX products.

Is Factor Still Relevant?

With the promise of gene therapy and other advancements, will prophylaxis factor be a thing of the past?

BY JENNIFER LARSON, FREELANCE WRITER
**Gene Therapy Promise and Limitations**

Here’s why factor is here to stay:

The idea of gene therapy is that a functional gene is inserted that establishes the production of factor VIII or IX, with the goal of reducing or eliminating the need to get repeated infusions of factor.

Here’s how gene therapy works in the advanced clinical trial state:

A modified virus is used to deliver a copy of the functional gene. According to a March 2021 article in the journal Hemasphere, recombinant adeno-associated viral (AAV) vectors have recently been “the predominant transgene delivery vehicle being used in hemophilia clinical gene therapy studies, an approach thought to be largely nonintegrating into the host genome.”

Once the functional gene begins to express the missing factor, the factor levels would begin to rise. Ideally, a person with severe hemophilia would see their clotting factor levels rise dramatically as the result of undergoing some type of gene therapy. No longer would they have to worry as much about their factor levels and the possibility of spontaneous bleeds.

However, the therapy does not alter the genetic code, so people will still be genetic carriers of hemophilia, able to pass it on to their children. Also, the therapy may degrade over time, and there are many questions about who will be eligible for gene therapy. (See gene therapy article on page 12.)

Numerous gene therapy clinical trials have been going on for decades, but nothing has been commercially available. But recently, some experts have suggested that hemophilia gene therapy products could hit the market soon. In 2020, two products looked close: BioMarin’s Roctavian for hemophilia A and uniQure’s AMT-061 for hemophilia B. But questions about both products interrupted their momentum.

The question of “when” is still an unknown, though. As Joe Pugliese, president and CEO of Hemophilia Alliance, said, “Gene therapy has been right around the corner for years.”

Until gene therapy products are available for a wide group of people with bleeding disorders, many will still need to prophylactically infuse—or at least now how to infuse and have easy access to factor.

**Until gene therapy products are available for a wide group of people with bleeding disorders, many will still need to prophylactically infuse—or at least know how to infuse and have easy access to factor.**

**People with mild and moderate hemophilia A or B.** Many hemophilia gene therapy clinical trials involve patients with severe or moderate-to-severe disease.

**People with hemophilia A or B with inhibitors.** About 1 in 5 people with hemophilia A and 3 in 100 with hemophilia B will develop inhibitors, or antibodies, in response to their treatments, according to the Centers for Disease Control and Prevention.

Those with inhibitors cannot use standard clotting factor treatment, and they may not be eligible for certain gene therapy products for some time, as very few clinical trials are investigating gene therapy in people affected by inhibitors.

**Women with hemophilia.** Most women with hemophilia have mild or moderate versions, while most gene therapy clinical trials are investigating products for severe hemophilia, which could leave women out for a while. Access to gene therapy products for women will eventually depend on how the U.S. Food and Drug Administration (FDA) licenses or approves products, according to Clark.

**Children with any severity of hemophilia A or B.** Those under 18 may not be eligible for gene therapy products for quite a while.

It’s also important to recognize that a person who undergoes gene therapy will likely still need factor replacement. The gene therapy product might only bring a person’s clotting levels up to mild or even moderate hemophilia, said pediatric hematologist Robert F. Sidonio Jr., MD, MSc, medical director of hemophilia, Aflac Cancer & Blood Disorders Center of Children’s Healthcare of Atlanta, and an associate professor at Emory University School of Medicine. In that case, they would still need to have access to factor, especially in the event of an injury or surgery.

Cost is also a factor that can’t be ignored. Factor therapy costs about $300,000 a year for someone with severe hemophilia—and the price is even higher for those with inhibitors. It remains to be seen how long a gene therapy treatment will last and whether the associated price tag will be higher or lower than the cost of factor—and how much of the cost will be covered by insurance.

“Right now, the mild or moderates will probably not be eligible for gene therapy, and the insurance companies will likely say it’s not worth trying to treat them with gene therapy.”

—David Clark, PhD

**Recombinant product for von Willebrand disease and the first factor X product.**

Then came Hemilbra, or emicizumab-kxwh, the first non-factor replacement therapy.

In 2017, the FDA approved emicizumab-kxwh injections for people with hemophilia A with factor VIII inhibitors, then in 2018 expanded the approval for routine prophylaxis to prevent or reduce bleeding in people with hemophilia A with or without factor VIII inhibitors. People who were eligible to use this bispecific monoclonal antibody no longer had to give themselves frequent intravenous factor infusions. Instead, they were looking at weekly, biweekly or even monthly subcutaneous injections instead.

Other products in development now hold a lot of promise, Clark said. One example: Sanofi’s BIvV001, which represents a new class of factor VIII replacement therapy. Phase 1/2a studies suggest that BIvV001 could achieve a three- or even four-fold increase in half-life, compared to conventional therapies, according to research published in September 2020 in the New England Journal of Medicine. While BIvV001 remains an intravenous injection, the half-life extension allows for once-weekly infusions, something people with factor VIII deficiency have yet to experience.

Furthermore, all of the currently available factor products on the market require intravenous infusion. But researchers are working on products that could be delivered by subcutaneous injection instead. One of these is Catalyst Biosciences’ Dalicencanog alfa (Dalca), which is in a Phase 2 clinical trial. The treatment will likely be daily, but a subcutaneous injection is easier for many people than accessing a vein for intravenous treatment, Long said.

If not complete game changers, these types of products could be time savers for many people with hemophilia—who are accustomed to carving out regular times in their day-to-day lives for prophy infusions.

But ultimately, “there’s nothing on the market or in the pipeline currently that would completely obviate the need for factor replacement in the future,” Sidonio said. “That’s just the bottom line.”

**“Right now, the mild or moderates will probably not be eligible for gene therapy, and the insurance companies will likely say it’s not worth trying to treat them with gene therapy.”**
The Future of Self-infusing?
One question that comes up often when considering advances in treatments for hemophilia is the future of self-infusions. Parents of children with hemophilia often learn how to give their children’s infusions until the children are old enough to learn how to do it themselves. Many parents and children learned how to do regular infusions through their hemophilia treatment centers (HTCs), home care or specialty pharmacies, or hemophilia summer camps.

“For some people, yes, they’re going to have to learn and maintain that skill set of self-infusion”
—Allison Wheeler, MD, MSCI

But if enough products come along that don’t require regular self-infusions, it’s possible that many people will lose the ability to give themselves infusions—or they may never learn how to do it in the first place. If their need for infused factor is just an infrequent occurrence, they might just visit their local emergency department or HTC or access home health services.

“For some people, yes, they’re going to have to learn and maintain that skill set of self-infusion,” said Allison Wheeler, MD, MSCI, a hematologist-oncologist and research director of the Vanderbilt Hemophilia Treatment Center in Nashville. But others won’t need to, she said, if a person only needs occasional infusions, they may not feel they need to learn how to give themselves infusion of factor. And that might be the right decision for them. If a person has a mild hemophilia phenotype, whether it’s the result of their mutation or the medications or treatments they take, it might be easier to find a medical provider who can aid in infusion instead of learning themselves. Plus, some products may not be available to some patients. And even if they are, some people may not choose to take advantage of them. For example, some people may choose gene therapy, while others might not.

Wheeler said she plans to show her patients the factor activity graphs and discuss their expectations with them. That can help patients decide if they’re satisfied with the therapies that they’re already using or if they want to try something new. That decision may also affect their decision about self-infusing and if that’s a skill that they want to master.

Sidonio acknowledged that with the acceleration of new therapies in recent years, self-infusing is already becoming a lost art for some people with hemophilia. But he does have some reservations about people not learning how to give themselves infusions and hopes that more people don’t completely discard that skill. “If you’re on a non-factor therapy, you will still need some therapy to elevate your factor levels to protect you from bleeding if you’re having surgery or in response to a bleeding event,” Sidonio said. “It’s a key to independence.”

The Future Role of HTCs
Currently, there are 145 HTCs in the United States and its territories. These critical treatment centers will continue to have an important place in the future, too, if they can continue to receive enough support from the patient community, Pugliese said.

HTCs will continue to be a resource for people who need factor replacement, especially those who can’t give themselves infusions or choose not to. But they can be a resource for people who opt to use newer products and emerging therapies, as well. Bleeding issues will still need to be monitored to ensure that a patient’s bleeding disorder is well-managed, regardless of treatment.

“They have the best expertise to make sure that gene therapy procedures are going to be successful,” Pugliese said. “I think it’s the most logical, safe and cost-effective way to do it: to work with the established experts in the field.”

What’s Next?
Now, we wait and see how well the emerging therapies, including gene therapy, deliver on their promises. For some, infused factor may become an infrequent event, while others may not have the choice to give up regular infusions. But all patients should continue to have a relationship with their HTC, Pugliese said.

And, at least for the foreseeable future, factor replacement therapy will continue to remain an important therapy for people with hemophilia. “If you’re on a non-factor therapy, you will still need some therapy to elevate your factor levels to protect you from bleeding if you’re having surgery or in response to a bleeding event,” Sidonio said.

In shared decision-making, the patient and/or their caregiver collaborates with their health care team. The patient talks about their needs and concerns while the treatment plan is created. Together, the team works to find the best fit for therapies and lifestyle changes that not only takes safety and efficacy into account but also patient preferences and goals.

Be a Part of the Team
Patients may find that having a treatment plan tailored to their lifestyle, preferences, and goals can be easier to follow. If the plan doesn’t fit into one’s lifestyle, it won’t offer the best chance at managing hemophilia well. When patients work closely with their health care team and are encouraged to communicate openly about treatment goals, it could lead to an improved quality of life.

The process of shared decision-making in treatment plans does mean that patients need to take some responsibility for their own care. However, being prepared for appointments and clearly discussing the impact of all the available treatment choices could lead to better experiences and outcomes.

Staying Plugged In
Part of being an empowered patient is being informed about research and advances in new treatments. People who live with hemophilia have choices when it comes to prophylactic, on-demand, and perioperative therapies. Advances in care and treatments for hemophilia are being made. Maintaining a connection with your care team to ask questions and get information about what options are right for you is key to staying informed. The staff at hemophilia treatment centers and hemophilia advocacy groups are good sources of information on clinical experiences, available treatments, and upcoming therapies.

Available Decision Tools
In the management of hemophilia, there are multiple therapies available. This is good from the aspect of patient choice, but it also means that putting together a plan takes more thought and effort. There may not be a clear-cut path to developing the “best” plan. This is why patient choice and comparing how options align with lifestyle and preferences becomes important. Researchers and patient advocacy groups have developed tools that can help health care providers and patients work together to decide on a plan. Some of these include:

• National Hemophilia Foundation: Products Licensed in the US, at www.nhf.org/hemophilia-products
• Hemophilia Federation of America Dateline Federation, at: www.pfizerpal.com

References

Taking the Lead
The health care team will often use a patient-centered approach that takes shared decision-making into account. However, in some cases, patients and/or caregivers may need to take a more active role in advocating for themselves and ensuring that their voices are heard.

Connecting with other patients and attending support groups is ways to learn more about how to engage more effectively with the health care team. Pfizer’s Patient Affairs Liaisons also can be a source of helpful information on shared decision-making; details on how to contact them can be found at the bottom of this page. Taking the time to understand hemophilia, what treatment options are available, and what one’s personal goals (and even family and friends’ goals) will all be a part of preparing for the shared decision-making process.

Visit www.pfizerpal.com to connect with your Patient Affairs Liaison.
Whether you or your child has just been diagnosed, or you’ve lived with a bleeding disorder for decades, knowledge of treatment options is a key component of being able to advocate for yourself and essential to having informed conversations with health care professionals. To help patients and caregivers with the process of navigating available treatment options, we’ve compiled a comprehensive list of all therapies currently available and approved by the Food and Drug Administration.

Information in this issue should not be interpreted as medical advice. We encourage frequent dialogue with experienced health care professionals regarding your health and the therapies used to treat your bleeding disorder.

### CURRENT PRODUCTS • BY THE NUMBERS

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### CURRENT PRODUCTS

#### List of Approved Products

Detailed product information can be found on the following pages, organized by indication.

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#### How to Navigate Our Product Charts

The pages that follow contain a comprehensive and exhaustive list of products that are approved by the Food and Drug Administration for treatment of a bleeding disorder. For ease of navigation, the charts are published in sections by indication (Factor VIII, Factor IX, Inhibitor, VWD, Rare or Other), with each containing the following categories of information:

- **Product**: Name used to market and sell the therapy.
- **Half-life**: Amount of time a product stays intact in the bloodstream until its efficacy is halved.
- **Manufacturer**: Company that produces and sells the therapy.
- **FDA Approved Year**: Year the product was approved for treatment by the FDA.
- **Indications**: Bleeding disorder type/factor deficiency the therapy is intended to treat.
- **Specific Product Type**: Detailed classification of product type, if applicable.

We’ve made every effort to ensure the accuracy of the information in this list by using information directly from manufacturers and publicly available information from websites such as the FDA’s. We do not encourage community members to use one product over another, and we strongly urge you to discuss your treatment options with qualified medical professionals.

Content in this issue is current as of March 2022. Given the fast-paced environment that manufacturers and governmental agencies work within, some information could have changed since going to print. Please refer to manufacturers’ or the FDA’s websites for the most up-to-date information.

#### FIND YOUR SECTION

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### Factor VIII

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<td>Advate</td>
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<td>Recombinant clotting factor</td>
<td>Antihemophilic Factor (Recombinant)</td>
<td>Adults (&gt;16 years): 12.0 ± 4.2 hrs; 12 to &lt;16 yrs: 12.0 ± 2.9; 5 to &lt;12 yrs: 11.2 ± 3.5 hrs; 2 to &lt;5 yrs: 9.5 ± 1.8 hrs; 1 month to &lt;2 yrs: 8.7 ± 1.4 hrs</td>
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<td>Adynovate</td>
<td>Takeda</td>
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<td>Antihemophilic Factor (Recombinant), PEGylated</td>
<td>18 years: 14.69 ± 3.79 hrs; 12 to &lt;18 years: 13.43 ± 4.05 hrs; 6 to &lt;12 years: 12.4 ± 1.67 hrs; &lt;6 years: 11.8 ± 2.43 hrs. Overall 1.3-1.5 half-life extension compared to ADVATE</td>
<td>2015</td>
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<tr>
<td>Afstyla</td>
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<td>Recombinant clotting factor</td>
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<td>After single dose of 50 IU/kg: Adults (&gt;18 years): 14.2 hours (mean); Adolescents (≥12 to &lt;18 years): 14.3 hours (mean); Children: (0 to &lt;6 yrs): 10.4 hours (mean); (≥6 to &lt;12 years): 10.2 hours (mean)</td>
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<td>Cyklokapron (tranexamic acid injection)</td>
<td>Pfizer</td>
<td>Non-factor product</td>
<td>Antifibrinolytic Agent</td>
<td>2 hours(^1)</td>
<td>1986</td>
<td>Factor VIII; Factor IX</td>
<td></td>
</tr>
<tr>
<td>DDAVP (Desmopressin)</td>
<td>Ferring Pharmaceuticals</td>
<td>Non-factor product</td>
<td>Intravenous Injection-Factor catalyst/factor booster/factor precipitator</td>
<td>1978</td>
<td>Factor VIII; VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desmopressin Acetate Injection USP (desmopressin acetate)</td>
<td>Dr. Reddy’s Laboratories</td>
<td>Non-factor product</td>
<td>Intravenous Injection-Factor catalyst/factor booster/factor precipitator</td>
<td>2020</td>
<td>Factor VIII; VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eloctate</td>
<td>Sanofi</td>
<td>Recombinant clotting factor</td>
<td>Antihemophilic Factor (Recombinant), Fc Fusion Protein</td>
<td>Adults - 19.7 hours (17.4, 22.0) Pediatric - 12 to 17 years: 16.4 hours (14.1, 18.8) 6 to 11 years: 14.9 hours (12.0, 17.8) 1 to 5 years: 12.7 hours (11.2, 14.1)</td>
<td>2014</td>
<td>Factor VIII</td>
<td></td>
</tr>
<tr>
<td>ESPEROCT</td>
<td>Novo Nordisk</td>
<td>Recombinant clotting factor</td>
<td>Glycopegylated</td>
<td>Single-dose 50 IU/kg: Adults: 21.7 hours Adolescents (12 to &lt;18 years old): 17.4 hours Children (6 to &lt;12 years old): 13.8 hours Children (1 to &lt;6 years old): 14.7 hours</td>
<td>2019</td>
<td>Factor VIII</td>
<td></td>
</tr>
</tbody>
</table>
### CURRENT PRODUCTS

<table>
<thead>
<tr>
<th>THERAPY NAME</th>
<th>MANUFACTURER</th>
<th>THERAPY TYPE</th>
<th>SPECIFIC THERAPY TYPE</th>
<th>HALF-LIFE</th>
<th>FDA APPROVAL</th>
<th>INDICATIONS/TARGET</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMLIBRA</td>
<td>Genentech</td>
<td>Bi-specific antibody</td>
<td>Therapeutic bi-specific antibody</td>
<td>26.9 +/- 9.1 days (mean +/- SD)</td>
<td>2017</td>
<td>Factor VIII; Inhibitor</td>
<td>&quot;2017 for inhibitors, 2018 for non-inhibitors Additional route of delivery information: humanized, monoclonal, subcutaneous injection&quot;</td>
</tr>
<tr>
<td>Hemofil M</td>
<td>Takeda</td>
<td>Plasma-derived clotting factor</td>
<td>Antihemophilic factor (human) method M, monoclonal purified</td>
<td>14.8 ± 3.0 hrs</td>
<td>1986</td>
<td>Factor VIII</td>
<td></td>
</tr>
<tr>
<td>Humate-P</td>
<td>CSL Behring</td>
<td>Plasma-derived clotting factor</td>
<td></td>
<td>12.2 hours (mean) in Hemophilia A; 10-11 hours (median) for VWD</td>
<td>1966</td>
<td>Factor VIII; VWD</td>
<td></td>
</tr>
<tr>
<td>Jivi</td>
<td>Bayer</td>
<td>Recombinant clotting factor</td>
<td>Antihemophilic factor (recombinant), PEGylated-antidi</td>
<td>17.9 hours Via chromogenic assay</td>
<td>2018</td>
<td>Factor VIII</td>
<td>Extended half-life</td>
</tr>
<tr>
<td>Koate</td>
<td>Kedrion Biopharma</td>
<td>Plasma-derived clotting factor</td>
<td></td>
<td>16.1</td>
<td>1974</td>
<td>Factor VIII</td>
<td></td>
</tr>
<tr>
<td>Kogenate FS</td>
<td>Bayer</td>
<td>Recombinant clotting factor</td>
<td>Antihemophilic factor (recombinant)</td>
<td>Adults: 13.74 hours Children: 10.7 hours</td>
<td>1993</td>
<td>Factor VIII</td>
<td></td>
</tr>
<tr>
<td>Kovaltry</td>
<td>Bayer</td>
<td>Recombinant clotting factor</td>
<td>Antihemophilic factor (recombinant)</td>
<td>0 to &lt;2 yrs: 9.6 hours 2 to &lt;6 yrs: 12.2 hours 6 to &lt;12 yrs: 12.0 hours 12 to 17 yrs: 14.4 hours &gt;18 yrs: 14.2 hours Via chromogenic substrate assay</td>
<td>2016</td>
<td>Factor VIII</td>
<td></td>
</tr>
<tr>
<td>Novoeight</td>
<td>Novo Nordisk</td>
<td>Recombinant clotting factor</td>
<td></td>
<td>Single-dose 50 IU/kg (adults/adolescents): One Stage Clotting Assay-10.8 hours, Chromogenic Assay-12.0 hours. Single-dose 50 IU/kg (pediatrics): One Stage Clotting Assay-0 to &lt;6 years old: 7.7 hours, 6 to &lt;12 years old: 8.0 hours. Chromogenic Assay-0 to &lt;6 years old: 10.0 hours, 6 to &lt;12 years old: 9.4 hours</td>
<td>2013</td>
<td>Factor VIII</td>
<td></td>
</tr>
<tr>
<td>NUWIQ</td>
<td>Octapharma USA</td>
<td>Recombinant clotting factor</td>
<td>Antihemophilic recombinant clotting factor</td>
<td>17.1 +/- 11.2hrs. (Adults); 13.1 +/- 2.6hrs. (6-12 yrs.); 11.9 +/- 5.4hrs. (2-5 yrs.)</td>
<td>2015</td>
<td>Factor VIII</td>
<td>NUWIQ is a recombinant FVIII produced in human cells without chemical modification or protein fusion. PUP data added to U.S. label in 2020</td>
</tr>
<tr>
<td>Recombinate</td>
<td>Takeda</td>
<td>Recombinant clotting factor</td>
<td>Antihemophilic factor (recombinant)</td>
<td>14.6 ± 4.9 hrs</td>
<td>1992</td>
<td>Factor VIII</td>
<td>Half-Life 11.2 ± 2.5 vs Advate</td>
</tr>
<tr>
<td>Stimate</td>
<td>Ferring Pharmaceuticals</td>
<td>Non-factor product</td>
<td>Nasal spray</td>
<td>3.3-3.5 hours</td>
<td>1994</td>
<td>Factor VIII; VWD</td>
<td>In February 2021, Ferring Pharmaceuticals stated that it did not anticipate restarting manufacturing and market delivery of STIMATE® before the second half of 2023, contingent on FDA approval</td>
</tr>
<tr>
<td>Wilate</td>
<td>Octapharma USA</td>
<td>Plasma-derived clotting factor</td>
<td></td>
<td>VWF: 15.8 hours; FVIII: 19.6 hours</td>
<td>2009</td>
<td>Factor VIII; VWD</td>
<td>Prophylaxis trial underway</td>
</tr>
</tbody>
</table>
### Factor VIII

<table>
<thead>
<tr>
<th>THERAPY NAME</th>
<th>MANUFACTURER</th>
<th>THERAPY TYPE</th>
<th>SPECIFIC THERAPY TYPE</th>
<th>HALF-LIFE</th>
<th>FDA APPROVAL</th>
<th>INDICATIONS/TARGET</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyntha</td>
<td>Pfizer</td>
<td>Recombinant clotting factor</td>
<td>Coagulation Factor VIII (recombinant)</td>
<td>11.2 ± 5.0 hours</td>
<td>2008</td>
<td>Factor VIII</td>
<td>1-Results from 30 previously treated patients (PTPs) 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA. 2-Compared to adults, the half-life of XYNTHA is shorter in children and the clearance (based on per kg body weight) is approximate. Prescribing Information at <a href="http://www.pfizermedicalinformation.com/en-us/patient">www.pfizermedicalinformation.com/en-us/patient</a></td>
</tr>
<tr>
<td>Xyntha Solofuse</td>
<td>Pfizer</td>
<td>Recombinant clotting factor</td>
<td>Coagulation Factor VIII (recombinant)</td>
<td>11.2 ± 5.0 hours</td>
<td>2008</td>
<td>Factor VIII</td>
<td>1-Results from 30 previously treated patients (PTPs) 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA. 2-Compared to adults, the half-life of XYNTHA is shorter in children and the clearance (based on per kg body weight) is approximate. Prescribing Information at <a href="http://www.pfizermedicalinformation.com/en-us/patient">www.pfizermedicalinformation.com/en-us/patient</a></td>
</tr>
</tbody>
</table>

### Factor IX

<table>
<thead>
<tr>
<th>THERAPY NAME</th>
<th>MANUFACTURER</th>
<th>THERAPY TYPE</th>
<th>SPECIFIC THERAPY TYPE</th>
<th>HALF-LIFE</th>
<th>FDA APPROVAL</th>
<th>INDICATIONS/TARGET</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphanine SD</td>
<td>Grifols</td>
<td>Plasma-derived clotting factor</td>
<td>Antihemophilic factor (recombinant), Fc fusion protein</td>
<td>50 IU/KG: Adults - 86.52 Hrs (37.2%); Pediatric - 12 to 17 years: 80 hours (35%); 6 to 11 years: 72 hours (23%); 2 to 5 years: 68 hours (24%); &lt; 10 IU/KG: Adults - 97 Hrs (35%); Pediatric - 12 to 17 years: 94 hours (24%)</td>
<td>1990</td>
<td>Factor IX</td>
<td></td>
</tr>
<tr>
<td>Alprolix</td>
<td>Sanofi</td>
<td>Recombinant clotting factor</td>
<td>Coagulation Factor IX (recombinant)</td>
<td>18.8 ± 5.4 hours (range 11 to 36 hours)</td>
<td>2014</td>
<td>Factor IX</td>
<td></td>
</tr>
<tr>
<td>BeneFIX</td>
<td>Pfizer</td>
<td>Recombinant clotting factor</td>
<td>Coagulation Factor IX (recombinant)</td>
<td>18.8 ± 5.4 hours (range 11 to 36 hours)</td>
<td>1997</td>
<td>Factor IX</td>
<td>1-Results from 37 previously treated adult patients (&gt;15 years old) after single intravenous dose of 50 IU/kg BeneFIX given as a 10-minute infusion. 2-The mean ± standard deviation ±SD in 13 children aged 2 years to &lt;12 years and 6 adolescents aged &gt;1</td>
</tr>
<tr>
<td>Cyklokapron (tranexamic acid injection)</td>
<td>Pfizer</td>
<td>Non-factor product</td>
<td>Antifibrinolytic agent</td>
<td>2 hours</td>
<td>1986</td>
<td>Factor VIII; Factor IX</td>
<td>1-Terminal elimination phase 2-indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction</td>
</tr>
</tbody>
</table>
### Factor IX

<table>
<thead>
<tr>
<th>THERAPY NAME</th>
<th>MANUFACTURER</th>
<th>THERAPY TYPE</th>
<th>SPECIFIC THERAPY TYPE</th>
<th>HALF-LIFE</th>
<th>FDA APPROVAL</th>
<th>INDICATIONS/TARGET</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelvion</td>
<td>CSL Behring</td>
<td>Recombinant clotting factor</td>
<td></td>
<td>After single dose of 50 IU/kg: Adults: 104 hours; Adolescents (12 to &lt;18 years): 87 hours (mean); Children: (0 to &lt;6 years): 90 hours (mean); and (6 to &lt;12 years): 93 hours (mean)</td>
<td>2016</td>
<td>Factor IX</td>
<td></td>
</tr>
<tr>
<td>IXINITY</td>
<td>Medexus</td>
<td>Recombinant clotting factor</td>
<td></td>
<td>24 hours</td>
<td>2015</td>
<td>Factor IX</td>
<td>Pediatric trial underway</td>
</tr>
<tr>
<td>Profilnine</td>
<td>Grifols</td>
<td>Plasma-derived clotting factor</td>
<td>Glycopegylated</td>
<td></td>
<td>1990</td>
<td>Factor IX</td>
<td></td>
</tr>
<tr>
<td>REBINYN</td>
<td>Novo Nordisk</td>
<td>Recombinant clotting factor</td>
<td></td>
<td>Single dose 40 IU/kg Adults (&gt;18 years old): 83.0 hours Adolescents (13-17 years old): 89.4 hours Children (7-12 years old): 76.3 hours Children (&lt;6 years old): 69.6 hours</td>
<td>2017</td>
<td>Factor IX</td>
<td></td>
</tr>
<tr>
<td>Rixibis</td>
<td>Takeda</td>
<td>Recombinant clotting factor</td>
<td>Coagulation Factor IX (recombinant)</td>
<td>±12 years= 25.7 ± 1.5 hrs; 6-&lt;12 years= 23.2 ± 1.6 hrs; &lt;6 years= 27.7 ± 2.7 hrs</td>
<td>2013</td>
<td>Factor IX</td>
<td></td>
</tr>
</tbody>
</table>

### Inhibitor

<table>
<thead>
<tr>
<th>THERAPY NAME</th>
<th>MANUFACTURER</th>
<th>THERAPY TYPE</th>
<th>SPECIFIC THERAPY TYPE</th>
<th>HALF-LIFE</th>
<th>FDA APPROVAL</th>
<th>INDICATIONS/TARGET</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEIBA NF</td>
<td>Takeda</td>
<td>Plasma-derived clotting factor</td>
<td>Anti-inhibitor coagulant complex</td>
<td>Peak thrombin generation at 15 to 30 minutes with thrombin generation returning to baseline value 8 to 12 hours, half-life is approximately 4-7 hours</td>
<td>1986</td>
<td>Inhibitor</td>
<td>Prophylaxis indication 2013. Plasma-derived clotting factor containing primarily non-activated FII, FIX and FX and activated FVIII, and small amounts of FVIII antigen</td>
</tr>
<tr>
<td>HEMLIBRA</td>
<td>Genentech</td>
<td>Bi-Specific antibody</td>
<td>Therapeutic bi-specific antibody</td>
<td>26.9 +/- 91 days (mean +/- SD)</td>
<td>2017</td>
<td>Factor VIII; Inhibitor</td>
<td>&quot;2017 for inhibitors, 2018 for non-inhibitors Additional route of delivery information: humanized, monoclonal, subcutaneous injection&quot; Additional route of delivery information: humanized, monoclonal, subcutaneous injection</td>
</tr>
<tr>
<td>NovoSeven RT</td>
<td>Novo Nordisk</td>
<td>Recombinant clotting factor</td>
<td></td>
<td>Hemophilia A (with and without inhibitors), Hemophilia B: Adolescents/Adults (15-63 years old): 2.72-3.3 hours, Pediatrics (2-12 years old): 1.9-3 hours, FVII Deficiency: Adults (20-45 years old): 2.62 hours</td>
<td>1999</td>
<td>Inhibitor; Rare</td>
<td></td>
</tr>
<tr>
<td>SEVENFACT</td>
<td>HEMA Biologics</td>
<td>Recombinant clotting factor</td>
<td>Recombinant Factor VIII</td>
<td>Hemophilia A or B: 225 mcg/kg dose - 1.4 hrs, 75mcg/kg dose - 1.7 hrs</td>
<td>2020</td>
<td>Inhibitor</td>
<td>Received FDA approval in April 2020. Now available as of January 2021.</td>
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</table>
## CURRENT PRODUCTS

### VWD

<table>
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<tr>
<th>THERAPY NAME</th>
<th>MANUFACTURER</th>
<th>THERAPY TYPE</th>
<th>SPECIFIC THERAPY TYPE</th>
<th>HALF-LIFE</th>
<th>FDA APPROVAL</th>
<th>INDICATIONS/TARGET</th>
<th>NOTES</th>
</tr>
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<tbody>
<tr>
<td><strong>Alphanate</strong></td>
<td>Grifols</td>
<td>Plasma-derived clotting factor</td>
<td>17.9</td>
<td>1978</td>
<td>Factor VIII; VWD with exceptions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DDAVP (Desmopressin)</strong></td>
<td>Ferring Pharmaceuticals</td>
<td>Non-factor product</td>
<td>Intravenous injection-factor catalyst/factor booster/factor precipitator</td>
<td>1978</td>
<td>Factor VIII; VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Desmopressin Acetate Injection USP (desmopressin acetate)</strong></td>
<td>Dr.Reddy's Laboratories</td>
<td>Non-factor product</td>
<td>Intravenous injection-factor catalyst/factor booster/factor precipitator</td>
<td>2020</td>
<td>Factor VIII; VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Humate-P</strong></td>
<td>CSL Behring</td>
<td>Plasma-derived clotting factor</td>
<td>12.2 hours (mean) in Hemophilia A; 10-11 hours (median) for VWD</td>
<td>1986</td>
<td>Factor VIII; VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stimate (Desmopressin Nasal Spray)</strong></td>
<td>Ferring Pharmaceuticals</td>
<td>Non-factor product</td>
<td>Nasal spray</td>
<td>1994</td>
<td>Factor VIII; VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vonvendi</strong></td>
<td>Takeda</td>
<td>Recombinant clotting factor</td>
<td>von Willebrand factor (recombinant)</td>
<td>2015</td>
<td>VWD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wilate</strong></td>
<td>Octapharma USA</td>
<td>Plasma-derived clotting factor</td>
<td>VWF: 15.8 hours; FVIII: 19.6 hours</td>
<td>2009</td>
<td>Factor VIII; VWD</td>
<td>Prophylaxis trial underway</td>
<td></td>
</tr>
</tbody>
</table>

### Other

<table>
<thead>
<tr>
<th>THERAPY NAME</th>
<th>MANUFACTURER</th>
<th>THERAPY TYPE</th>
<th>SPECIFIC THERAPY TYPE</th>
<th>HALF-LIFE</th>
<th>FDA APPROVAL</th>
<th>INDICATIONS/TARGET</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amicar (amniocaproic acid—oral solution and tablets)</strong></td>
<td>Akorn Pharmaceuticals</td>
<td>Non-factor product</td>
<td>Oral solution and tablets</td>
<td>n/a</td>
<td>1998</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td><strong>Lysteda (tranexamic acid tablets)</strong></td>
<td>Ferring Pharmaceuticals</td>
<td>Non-factor product</td>
<td>Tablet</td>
<td>n/a</td>
<td>1986</td>
<td>Other</td>
<td>Tablet/650mg</td>
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</tbody>
</table>
## Current Products

<table>
<thead>
<tr>
<th>Therapy Name</th>
<th>Manufacturer</th>
<th>Therapy Type</th>
<th>Specific Therapy Type</th>
<th>Half-Life</th>
<th>FDA Approval</th>
<th>Indications/Target</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagadex</td>
<td>Bio Products Laboratory USA</td>
<td>Plasma-derived clotting factor</td>
<td>Lyophilized powder for solution for intravenous injection</td>
<td>Patients 12 years and older: 30.3 hours Children &lt; 12 years: *See Public Notes</td>
<td>2015</td>
<td>Rare</td>
<td>* The half-life in children &lt;12 years has not been evaluated. However, incremental recovery (IR) in children &lt;12 years of age has been assessed and is significantly lower than in patients 12 years and older, translating to larger dosing requirements in this age group, as per the approved dosing recommendations in the Coagadex label. In a phase 3 study in children aged &lt;12 years diagnosed with moderate or severe hereditary FXD, the mean IR was significantly lower in younger (0-5 years) than in older (6-11 years) children (1.53 vs 1.91 IU/dL per IU/kg; p = 0.001). In the overall population of children 0 - 11 years, mean IR was 1.74 IU/dL per IU/kg. In patients 12 years and older, IR has been assessed to be significantly higher at 2.04 IU/dL per IU/kg.</td>
</tr>
<tr>
<td>Corifact</td>
<td>CSL Behring</td>
<td>Plasma-derived clotting factor</td>
<td></td>
<td>6.6 hours by Berichrom Assay method (mean)</td>
<td>2011</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>FIBRYGA</td>
<td>Octapharma USA</td>
<td>Plasma-derived clotting factor</td>
<td></td>
<td>75.9 hours (mean)</td>
<td>2017</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>NovoSeven RT</td>
<td>Novo Nordisk</td>
<td>Recombinant clotting factor</td>
<td>Hemophilia A (with and without inhibitors), Hemophilia B: Adolescents/Adults (15-65 years old): 2.72-3.3 hours, Pediatrics (2-12 years old): 1.9-3 hours. FVII Deficiency: Adults (20-43 years old): 2.62 hours</td>
<td></td>
<td>1999</td>
<td>Inhibitor; Rare</td>
<td></td>
</tr>
<tr>
<td>Obizur</td>
<td>Takeda</td>
<td>Recombinant clotting factor</td>
<td>Antihemophilic factor (recombinant), porcine sequence</td>
<td>Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses</td>
<td>2014</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>RiaSTAP</td>
<td>CSL Behring</td>
<td>Plasma-derived clotting factor</td>
<td></td>
<td>78.7 hours (mean)</td>
<td>2009</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Tretten</td>
<td>Novo Nordisk</td>
<td>Recombinant clotting factor</td>
<td>Steady state baseline adjusted FXIII activity: 5.1 days Single dose baseline adjusted FXIII activity (pediatrics [1 to &lt;6 years old]): 7.1 days</td>
<td></td>
<td>2013</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>
We can’t wait to see you again!

Until then, we’re here for you and your family at www.hemophiliafed.org

A ONCE-WEEKLY TREATMENT OPTION FOR HEMOPHILIA B.

HOW DOES THIS FACTOR IN?

To find out about a prescription option, talk to your doctor or visit OnceWeeklyForHemophiliaB.com
**US Food and Drug Administration’s Drug Approval Process**

**What is a drug, as defined by the FDA?**

A drug is any product that is intended for the use in the diagnosis, cure, mitigation, treatment or prevention of disease and is intended to affect the structure or any function of the body.

**PRE-CLINICAL**

*Drug Sponsor's Discovery and Screening Phase:*

1. **Drug Developed**
   - Drug sponsor develops a new drug compound and seeks to have it approved by the FDA for sale in the United States.

2. **Animals Tested**
   - Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

3. **IND Application**
   - The sponsor submits an investigational new drug (IND) application to the FDA based on the results from initial testing. This application includes the drug’s composition and manufacturing specifications and offers a plan for testing the drug on humans.

4. **IND Review**
   - The FDA reviews the IND to ensure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protections.

5. **CLINICAL**

   *Drug Sponsor’s Clinical Studies/Trials:*

   - **Phase 1**
     - 20–80: The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal in this phase is to determine what the drug’s most frequent side effects are and, often, how the drug is metabolized and excreted.

   - **Phase 2**
     - 100s: The typical number of patients used in Phase 2; this phase emphasizes effectiveness. The goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo or a different drug. Safety continues to be evaluated, and short-term side effects are studied. At the end of Phase 2, the FDA and sponsors discuss how large-scale studies in Phase 3 will be conducted.

   - **Phase 3**
     - 1,000s: The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and use the drug in combination with other drugs.

6. **NDA REVIEW**

   *FDA’s New Drug Application Review:*

   - **Review Meeting**
     - The FDA meets with a drug sponsor prior to submission of a new drug application.

   - **NDA Application**
     - The drug sponsor formally asks the FDA to approve a drug for marketing in the U.S. by submitting a new drug application (NDA). An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

   - **Application Reviewed**
     - After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor’s research on the drug’s safety and effectiveness.

   - **Drug Labeling**
     - The FDA reviews the drug’s professional labeling and ensures appropriate information is communicated to health care professionals and consumers.

7. **POST-MARKETING**

   *FDA’s Post-Approval Risk Assessment Systems:*

   - **Phase 4**
     - Because it’s not possible to predict all of a drug’s effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of the FDA’s post-marketing safety system is meant to detect serious unexpected adverse events and take definitive action when needed.

   - **Drug Approval**
     - The FDA reviewers will approve the application or issue a complete response letter, which will describe the specific deficiencies that the agency has identified in an application.

   - **Facility Inspection**
     - The FDA inspectors the facilities where the drug will be manufactured.

   - **Drug Approval**
     - The FDA reviewers will approve the application or issue a complete response letter, which will describe the specific deficiencies that the agency has identified in an application.

   - **Facility Inspection**
     - The FDA reviews the facilities where the drug will be manufactured.

   - **Drug Approval**
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   - **Facility Inspection**
     - The FDA reviews the facilities where the drug will be manufactured.

8. **Facility Inspection**

   - The FDA inspects the facilities where the drug will be manufactured.

9. **Drug Approval**

   - The FDA reviewers will approve the application or issue a complete response letter, which will describe the specific deficiencies that the agency has identified in an application.

10. **Drug Approval**

    - The FDA reviewers will approve the application or issue a complete response letter, which will describe the specific deficiencies that the agency has identified in an application.

11. **Drug Approval**

    - The FDA reviewers will approve the application or issue a complete response letter, which will describe the specific deficiencies that the agency has identified in an application.

12. **Facility Inspection**

    - The FDA reviews the facilities where the drug will be manufactured.

13. **Drug Approval**

    - The FDA reviewers will approve the application or issue a complete response letter, which will describe the specific deficiencies that the agency has identified in an application.

14. **Drug Approval**

    - The FDA reviewers will approve the application or issue a complete response letter, which will describe the specific deficiencies that the agency has identified in an application.

The FDA’s requirement for the number of patients needed to conduct a study/trial does change based on the size of the patient population being studied. For bleeding disorder studies/trials, counts are significantly reduced and sometimes can be fewer than 10 patients for Phase I trials. By Phase III, trials may include more than 100 people.

The objective: have a statistically relevant sample size from which to draw conclusions.

For example, 200 trial participants in a hemophilia study is 1% of the U.S. hemophilia population, whereas 1% of the U.S. diabetic population in a diabetes study trial would equal 291,000 participants.

The FDA’s requirement for the number of patients needed to conduct a study/trial does change based on the size of the patient population being studied. For bleeding disorder studies/trials, counts are significantly reduced and sometimes can be fewer than 10 patients for Phase I trials. By Phase III, trials may include more than 100 people.

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For example, 200 trial participants in a hemophilia study is 1% of the U.S. hemophilia population, whereas 1% of the U.S. diabetic population in a diabetes study trial would equal 291,000 participants.
The aim of this study is to find out how common it is for people with hemophilia A to have existing antibodies against adeno-associated virus (AAV) and what it could mean for the development of future treatments.

By participating, you can help us understand how the body may develop antibodies against the naturally occurring AAV.

You may qualify for the SAAVY (270-701) study if:
- You are 18 years of age or older; and
- You have a diagnosis of hemophilia A

How does the study work?
- Participants will be asked to complete 2 blood draws and answer questions on a convenient mobile app.
- You’ll receive compensation after each blood donation for your time and participation.
- No medication, therapy, or experimental procedures are part of this study.

What value will the results of the study bring to the hemophilia community?
Different types of AAV are frequently used in clinical trials for gene therapy. Understanding the presence of AAV antibodies will help guide researchers in developing innovative therapies for people with hemophilia A.

Curious about how a therapeutic vector is built and what the eligibility requirements for gene therapy research may be? Sign up for the BioMarin Gene Therapy Learning Academy to get more details about gene therapy research delivered straight to your inbox.
EMERGING THERAPIES

AVAILABLE FOR TREATMENT OF BLEEDING DISORDERS

Within the past decade alone, medical research and scientific advancements have reshaped the way the bleeding disorders community looks at treatment. Discussions of a cure, or long-lasting, one-time treatment options no longer seem so far-fetched, but they are instead very likely outcomes of a scientific breakthrough. Numerous companies and research teams are evaluating their products and therapies through the Food and Drug Administration’s (FDA’s) clinical trial process right now.

Whether you or your child has just been diagnosed, or you’ve lived with a bleeding disorder for decades, knowledge of approved treatment options and emerging therapies is a key component of being able to advocate for yourself and essential to have informed conversations with health care professionals. To help patients and caregivers with the process of navigating emerging therapies, we’ve compiled a comprehensive list of therapies currently undergoing clinical trial through FDA.

Information in this issue should not be interpreted as medical advice. We encourage frequent dialogue with experienced health care professionals regarding your health and the therapies used to treat your bleeding disorder.

Investigational Therapeutic Products Currently Undergoing Clinical Trial

Detailed product information can be found on the following pages, organized by indication.

- AAV2/8-HLP-FVIII-V3
  - Factor VIII
- AAVS-hFIXco-Padua / AMT-061
  - Factor IX
- AMT-060 (AAV5-hFIX)
  - Factor IX
- APVO101 (IXINITY)
  - Factor IX
- BAY2599023 (DTX201)
  - Factor VIII
- Coagulation FVIIa (Recombinant) Eptacog Beta or LR769
  - Inhibitor
- concizumab
  - Factor VIII; Factor IX
- Dalcinonacog alfa (CB 2679d/ISU304)
  - Inhibitor
- Efanesoctocog Alfa (BIVV001)
  - Factor VIII
- Fidanacogene elaparovvec
  - Factor IX
- Fitusiran/SAR439774
  - Factor VIII; Factor IX; Inhibitor
- FLT180a
  - Factor IX
- giroctocogene fitelparvovec
  - Factor VIII
- giroctocogene fitelparvovec, fidanacogene elaparovvec
  - Factor VIII; Factor IX
- Marstacimab
  - Factor VIII; Factor IX; Inhibitor
- Marzeptacog alfa (activatcd)
  - Factor IX
- MOD-5014
  - Factor IX; Rare
- NNC0365-3769 A (Mim8)
  - Factor VIII; Inhibitor
- SB-525
  - Factor VIII
- SB-FIX
  - Factor VIII
- scAAV2/8-LPI-hFIXco
  - Factor IX
- SCT800
  - Factor VIII
- SIG-001
  - Factor VIII
- SPK-8011
  - Factor VIII
- SPK-8016
  - Factor VIII
- SubQ-8
  - Factor VIII
- TAK-748
  - Factor IX
- TAK-754
  - Factor VIII
- TAK-755
  - Rare
- valoctocogene roxaparvovec
  - Factor VIII
How To Navigate Our Emerging Therapies Charts

The pages that follow contain a list of emerging therapies that are undergoing clinical trial by the Food and Drug Administration (FDA) for treatment of a bleeding disorder. For ease of navigation, the charts are published in sections by type of product—gene therapy, novel, recombinant clotting factor—with each containing the following categories of information:

- **Investigational Therapeutic Product Name**: Product name used during a research/trial. Usually, this name is changed when a product is approved and brought to market.
- **FDA Status and Phase**: Phase of clinical trial.
- **Indication Details**: Detailed classification of indication, if applicable.
- **Sponsor**: Company that is researching/studying a product/trial.
- **Official Study Title**: Submitted to the FDA for clinical trial usage.

We’ve made every effort to ensure the accuracy of the information in this list by using information directly from manufacturers and publicly available information from websites such as the FDA’s. We do not encourage community members to use one product over another, and we strongly urge you to discuss your treatment options with qualified medical professionals.

Content in this issue is current as of March 2022. Given the fast-paced environment that manufacturers and governmental agencies work within, some information could have changed since going to print. Please refer to manufacturers’ or the FDA’s websites for the most up-to-date information.

### Pharmaceuticals

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<tr>
<th>Type of Investigational Therapeutic Product Undergoing Trial</th>
<th>29 Investigational Therapeutic Products In 53 Clinical Trials</th>
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<td>Gene Therapy..........................................................</td>
<td>Sanofi Genzyme .................................................12</td>
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<td>Novel: Investigational Factor Product ..................................</td>
<td>Pfizer Inc. ..................................................6</td>
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<tr>
<td>Novel: Non-factor product ....................................................</td>
<td>Biomarin Pharmaceutical ...................................5</td>
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<tr>
<td>Recombinant Clotting Factor ................................................</td>
<td>Hema Biologics ................................................3</td>
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<td>Novo Nordisk ......................................................................3</td>
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<td>Takeda ..............................................................................3</td>
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<td>CSL Behring/uniQure .......................................................3</td>
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<tr>
<td><strong>Companies Running the Most Trials</strong></td>
<td><strong>Clinical Trials By Indication</strong></td>
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<tr>
<td>Sanofi Genzyme .................................................12</td>
<td><strong>Factor VIII</strong></td>
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<tr>
<td>Pfizer Inc. ..................................................6</td>
<td><strong>RARE</strong></td>
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<tr>
<td>Biomarin Pharmaceutical ...................................5</td>
<td><strong>Factor IX</strong></td>
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<tr>
<td>Hema Biologics ................................................3</td>
<td><strong>Factor VIII</strong></td>
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<tr>
<td>Novo Nordisk ......................................................................3</td>
<td><strong>Factor IX</strong></td>
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<td>Takeda ..............................................................................3</td>
<td><strong>Factor VIII</strong></td>
</tr>
<tr>
<td>CSL Behring/uniQure .......................................................3</td>
<td><strong>RARE</strong></td>
</tr>
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</table>

### Clinical Trials by Indication

- **Factor VIII**: 38
- **RARE**: 4

*Note: One clinical trial can research more than one indication.

### Stages of Ongoing Clinical Trials

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<tr>
<th>Phase</th>
<th>Number</th>
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<td>PHASE 1</td>
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<td>PHASE 1/2</td>
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<td>PHASE 2</td>
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<td>PHASE 2/3</td>
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<td>PHASE 3</td>
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<td>PHASE 3/4</td>
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<tr>
<td>PHASE 4</td>
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</table>

**FIND YOUR SECTION**

<table>
<thead>
<tr>
<th>Type of Investigational Therapeutic Product</th>
<th>Novel: Investigational Factor Product</th>
<th>Novel: Non-factor product</th>
<th>Recombinant Clotting Factor</th>
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<tbody>
<tr>
<td><strong>Factor VIII</strong></td>
<td><strong>Factor IX</strong></td>
<td><strong>Factor VIII</strong></td>
<td><strong>Factor IX</strong></td>
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<tr>
<td>52</td>
<td>56</td>
<td>60</td>
<td>62</td>
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</table>
## Gene Therapy • Factor VIII

<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>CLINICAL TRIAL ORGANIZATION NAME</th>
<th>SPECIFIC PRODUCT TYPE</th>
<th>FDA STATUS COMMENTS</th>
<th>INDICATION DETAILS</th>
<th>OFFICIAL STUDY TITLE</th>
<th>CLINICAL TRIAL NOTES</th>
<th>PUBLIC NOTES</th>
</tr>
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<tbody>
<tr>
<td>BAY2599023 (DTX201)</td>
<td>Bayer</td>
<td>AAV Vector-Mediated Gene Transfer Therapy</td>
<td>Phase 1/2 - Recruiting</td>
<td>Severe Hemophilia A</td>
<td>A Phase 1/2 Open-label Safety and Dose-finding Study of BAY2599023 (DTX201), an Adeno-associated Virus (AAV) hu37-mediated Gene Transfer of B-domain Deleted Human Factor VIII in Adults With Severe Hemophilia A</td>
<td>Recruiting by invitation</td>
<td>Bayer in collaboration with Ultragenyx Pharmaceuticals</td>
</tr>
<tr>
<td>valoctocogene roxaparvovec</td>
<td>BioMarin Pharmaceutical Inc.</td>
<td>AAV Vector-Mediated Gene Transfer Therapy</td>
<td>Phase 3 - Orphan Drug Designation from FDA; Breakthrough Therapy Designation from FDA and EMA; PRIority MEdicines (PRIME) status from EMA; BLA filed to FDA Q4 2019; MAA validated by EMA Q4 2019.</td>
<td>Severe Hemophilia A</td>
<td>301 - A Phase 3 Open-Label, Single-Arm Study To Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII at a dose of 6E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL</td>
<td>Active, not enrolling</td>
<td></td>
</tr>
<tr>
<td>valoctocogene roxaparvovec</td>
<td>BioMarin Pharmaceutical Inc.</td>
<td>AAV Vector-Mediated Gene Transfer Therapy</td>
<td>Phase 3 - Orphan Drug Designation from FDA; Breakthrough Therapy Designation from FDA and EMA; PRIority MEdicines (PRIME) status from EMA; BLA filed to FDA Q4 2019; MAA validated by EMA Q4 2019.</td>
<td>Severe Hemophilia A</td>
<td>302 - A Phase 3 Open-Label, Single-Arm Study To Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII at a dose of 4E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL</td>
<td>Active, not enrolling</td>
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</tr>
<tr>
<td>valoctocogene roxaparvovec</td>
<td>BioMarin Pharmaceutical Inc.</td>
<td>AAV Vector-Mediated Gene Transfer Therapy</td>
<td>Phase 3 - Orphan Drug Designation from FDA; Breakthrough Therapy Designation from FDA and EMA; PRIority MEdicines (PRIME) status from EMA; BLA filed to FDA Q4 2019; MAA validated by EMA Q4 2019.</td>
<td>Severe Hemophilia A</td>
<td>303 - A Phase 3b, Single Arm, Open-Label Study to Evaluate The Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII with Prophylactic Corticosteroids in Hemophilia A Patients</td>
<td>Active and Enrolling</td>
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<tr>
<td>valoctocogene roxaparvovec</td>
<td>BioMarin Pharmaceutical Inc.</td>
<td>AAV Vector-Mediated Gene Transfer Therapy</td>
<td>Phase 1/2</td>
<td>Severe Hemophilia A</td>
<td>205 - A Phase 1/2 Safety, Tolerability, and Efficacy Study of BMN 270, an Adeno-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Active or Prior Inhibitors</td>
<td>Recruiting by invitation</td>
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<tr>
<td>valoctocogene roxaparvovec</td>
<td>BioMarin Pharmaceutical Inc.</td>
<td>Observational</td>
<td></td>
<td>Hemophilia A</td>
<td>701 - A Prospective, Observational Study Evaluating Seroprevalence and Rate of Seroconversion of Antibodies against Adeno-associated Virus (AAV) Serotypes and Exploratory Vectors in Subjects with Hemophilia A in the United States</td>
<td>Active and Enrolling</td>
<td></td>
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<tr>
<td>PRODUCT NAME</td>
<td>CLINICAL TRIAL PRODUCTS: ORGANIZATION NAME</td>
<td>SPECIFIC PRODUCT TYPE</td>
<td>FDA STATUS COMMENTS</td>
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<tr>
<td>fidanacogene elaparvovec; giroctocogene fitelparvovec</td>
<td>Pfizer, Inc.</td>
<td>Gene Transfer</td>
<td>Phase 3; not recruiting</td>
<td>Males 18 to 65 years of age with moderately severe to severe hemophilia A (FVIII:C &lt;1%) who are negative for nAb to AAV vector SB-525 capsid (AAV6) and moderately severe to severe hemophilia B (FIX:C &lt;2%) who are negative for nAb to AAV vector Spark-100.</td>
<td>Six Month lead-in Study to Evaluate Prospective Efficacy and Safety Data of Current FIX Prophylaxis Replacement Therapy in Adult Hemophilia B Subjects (FIX:C&lt;2%) or Current FVIII Prophylaxis Replacement Therapy in Adult Hemophilia A Subjects (FIX:C&lt;1%)</td>
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<tr>
<td>giroctocogene fitelparvovec</td>
<td>Pfizer, Inc.</td>
<td>Gene Transfer</td>
<td>Phase 3; not recruiting</td>
<td>Males 18 to 64 years of age with moderately severe to severe hemophilia A (FVIII:C &lt;1%) who have been followed on routine FVIII prophylaxis therapy during the lead-in study (C0371004) and have &gt; 150 documented exposure days to FVIII protein product.</td>
<td>Phase 3, open-label, single-arm study to evaluate the efficacy and safety of PF-07055480 (recombinant AAV2/6 human factor VIII gene therapy) in adult male participants with moderately severe to severe hemophilia A (FVIII:C&lt;1%)</td>
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<tr>
<td>giroctocogene fitelparvovec</td>
<td>Pfizer, Inc.</td>
<td>Gene Transfer</td>
<td>Phase 1/2; active, not recruiting</td>
<td>Males 18 years of age and older with severe hemophilia A (FVIII:C &lt;1%) who were treated or exposed to FVIII concentrates or cryoprecipitate for at least 150 exposure days; if receiving on demand therapy over the preceding 12 months has &gt;12 bleeding episodes.</td>
<td>A phase 1/2, open-label, adaptive, dose-ranging study to assess the safety and tolerability of SB-525 (PF-07055480) (recombinant AAV2/6 human factor 8 gene therapy) in adult subjects with severe hemophilia A</td>
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<tr>
<td>SB-FIX</td>
<td>Sangamo Therapeutics</td>
<td>Genome Editing</td>
<td>Phase 1 - IND cleared. Orphan drug designation by FDA</td>
<td>Severe IX</td>
<td>A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy Via Zinc Finger Nuclease (ZFN) Mediated Targeted Integration of SB-FIX in Adult Subjects With Severe Hemophilia B</td>
<td>Active, not recruiting</td>
<td>Sangamo Therapeutics, in partnership with Pfizer</td>
</tr>
<tr>
<td>SB-525</td>
<td>Sangamo Therapeutics</td>
<td>Genome Editing</td>
<td>Phase 1/2 - IND cleared. Orphan drug designation by FDA and EMA. Fast track from FDA</td>
<td>Severe VIII</td>
<td>A Phase 1/2, Open-Label, Adaptive, Dose-Ranging Study to Assess the Safety and Tolerability of SB-525 (Recombinant AAV2/6 Human Factor 8 Gene Therapy) in Adult Subjects With Severe Hemophilia A</td>
<td>Active, not recruiting</td>
<td>Pfizer</td>
</tr>
<tr>
<td>SPK-8016</td>
<td>Spark Therapeutics, Inc.</td>
<td>Gene Transfer</td>
<td>Phase 1, Phase 2</td>
<td>VIII</td>
<td>Dose-finding Study of SPK-8016 Gene Therapy in Patients With Hemophilia A to Support Evaluation in Individuals With FVIII Inhibitors</td>
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### Gene Therapy • Factor VIII

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<tr>
<th>PRODUCT NAME</th>
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<th>OFFICIAL STUDY TITLE</th>
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<tbody>
<tr>
<td>SPK-8011</td>
<td>Spark Therapeutics, Inc.</td>
<td>Gene Transfer</td>
<td>Phase 1, Phase 2</td>
<td>VIII</td>
<td>Gene Transfer, Dose-Finding Safety, Tolerability, and Efficacy Study of SPK-8011 [a Recombinant Adeno-Associated Viral Vector With Human Factor VIII Gene] in Individuals With Hemophilia A</td>
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<tr>
<td>AAV2/8-HLP-FVIII-V3</td>
<td>St. Jude Children’s Research Hospital</td>
<td>Gene Transfer</td>
<td>Phase 1</td>
<td>VIII</td>
<td>GO-B: Gene Therapy for Haemophilia A Using a Novel Serotype 8 Capsid Pseudotyped Adeno-associated Viral Vector Encoding Factor VIII-V3</td>
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### Gene Therapy • Factor IX

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<th>PRODUCT NAME</th>
<th>CLINICAL TRIAL PRODUCTS: ORGANIZATION NAME</th>
<th>SPECIFIC PRODUCT TYPE</th>
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<th>OFFICIAL STUDY TITLE</th>
<th>CLINICAL TRIAL NOTES</th>
<th>PUBLIC NOTES</th>
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<tbody>
<tr>
<td>AAVS-hFIXco-Padua/AMT-061</td>
<td>CSL Behring/uniQure</td>
<td>Gene Transfer</td>
<td>Phase 3 - Breakthrough Designation; 1/30/17</td>
<td>IX</td>
<td>Phase III, Open-label, Single-dose, Multi-center, Multinational Trial Investigating a Serotype 5 Adeno-associated Viral Vector Containing the Padua Variant of a Codon-optimized Human Factor IX Gene (AAVS-hFIXco-Padua, AMT-061) Administered to Adult Subjects</td>
<td>Licensed to CSL Behring for Commercialization (pending government approval), Trial on Clinical Hold FDA, Dec. 2020</td>
<td></td>
</tr>
<tr>
<td>AAVS-hFIXco-Padua/AMT-061</td>
<td>CSL Behring/uniQure</td>
<td>Gene Transfer</td>
<td>Phase 2B - Breakthrough Designation; 1/30/17</td>
<td>IX</td>
<td>Phase IIIb, Open-label, Single-dose, Single-arm, Multi-center Trial to Confirm the Factor IX Activity Level of the Serotype 5 Adeno-associated Viral Vector Containing the Padua Variant of a Codon-optimized Human Factor IX Gene (AAVS-hFIXco-Padua, AMT-061)</td>
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<tr>
<td>AMT-060 (AAAVS-hFIX)</td>
<td>CSL Behring/uniQure</td>
<td>Gene Transfer</td>
<td>Phase 1, Phase 2 - Breakthrough Designation; 1/30/17</td>
<td>IX</td>
<td>A Phase I/II, Open-label, Uncontrolled, Single-dose, Dose-ascending, Multi-centre Trial Investigating an Adeno-associated Viral Vector Containing a Codon-optimized Human Factor IX Gene (AAAVS-hFIX) Administered to Adult Patients With Severe or Moderately Severe Hemophilia B</td>
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<td>FLT180a</td>
<td>Freeline Therapeutics</td>
<td>Gene Transfer</td>
<td>Phase 1/2 - Open IND. Interventional study.</td>
<td>IX</td>
<td>A Factor IX Gene Therapy Study (FIX-GT) (FIX-GT)</td>
<td>ClinicalTrials.gov link: <a href="https://clinicaltrials.gov/ct2/show/NCT03369444?term=FLT180a&amp;rank=2">https://clinicaltrials.gov/ct2/show/NCT03369444?term=FLT180a&amp;rank=2</a></td>
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<tr>
<td>fidanacogene elaparvovec; giroctocogene fitelparvovec</td>
<td>Pfizer, Inc.</td>
<td>Gene Transfer</td>
<td>Phase 3; not recruiting</td>
<td>Males 18 to 65 years of age with moderately severe to severe hemophilia A (FVIII:C &lt;1%) who are negative for nAb to AAV vector SB-525 capsid (AAV6) and moderately severe to severe hemophilia B (FIX:C &lt;2%) who are negative for nAb to AAV vector Spark-100,</td>
<td>Six Month lead-in Study to Evaluate Prospective Efficacy and Safety Data of Current FIX Prophylaxis Replacement Therapy in Adult Hemophilia B Subjects (FIX:C&lt;2%) or Current FVIII Prophylaxis Replacement Therapy in Adult Hemophilia A Subjects (FIX:C&lt;1%)</td>
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<td>fidanacogene elaparvovec</td>
<td>Pfizer, Inc.</td>
<td>Gene Transfer</td>
<td>Phase 3; active, not recruiting</td>
<td>Males 18 to 65 years of age with moderately severe to severe hemophilia B (FIX:C&lt;2%) and no history of inhibitors who completed 6 months of routine Factor IX prophylaxis therapy during the lead-in study (C0371004) and have &gt;50 documented exposure days to</td>
<td>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)</td>
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<tr>
<td>fidanacogene elaparvovec</td>
<td>Pfizer, Inc.</td>
<td>Gene Transfer</td>
<td>Phase 2; recruiting</td>
<td>Males 18 to 65 years of age with moderately severe to severe hemophilia B (FIX:C&lt;2%) with &gt;50 exposure days and no history of inhibitors</td>
<td>Long-term Safety and Efficacy Study and Dose-Escalation Substudy of PF 06838435 in Individuals With Hemophilia B</td>
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<tr>
<td>scAAV2/8-LPI-hFIXco</td>
<td>St. Jude Children's Research Hospital</td>
<td>Gene Transfer</td>
<td>Phase 1</td>
<td>IX</td>
<td>An Open Label Dose-Escalation Study Of A Self Complementary Adeno-Associated Viral Vector (scAAV 2/8-LPI-hFIXco) For Gene Transfer in Hemophilia B</td>
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## Novel: Investigational factor product • Factor VIII

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<th>FDA STATUS COMMENTS</th>
<th>INDICATION DETAILS</th>
<th>OFFICIAL STUDY TITLE</th>
<th>CLINICAL TRIAL NOTES</th>
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<tr>
<td>MOD-5014</td>
<td>OPKO Biologics</td>
<td>Long-acting Recombinant VIIa</td>
<td>Phase 1</td>
<td>VIII, IX with inhibitors</td>
<td>A Phase 1 Randomized, Single-blind, Placebo-controlled, Single Dose, Dose-escalated Study to Assess the Safety, Pharmacokinetic and Pharmacodynamic Profile of Subcutaneous Administration of a Long-acting Recombinant Factor VIIa in Healthy Adult Males</td>
<td><strong>Novel</strong>: Investigational factor product • Factor VIII</td>
<td><strong>Novel</strong>: Investigational factor product • Factor VIII</td>
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<tr>
<td>Efanesoctocog Alfa (BIVV001)</td>
<td>Sanofi</td>
<td>rFVIIIFc-XTEN</td>
<td>Phase 3</td>
<td>FVIII</td>
<td>A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients ≥ 12 Years of Age</td>
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<td>rFVIIIFc-XTEN</td>
<td>Phase 3</td>
<td>FVIII</td>
<td>A Phase 3 Open-Label, Multicenter Study of the Long-term Safety and Efficacy of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients With Severe Hemophilia</td>
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<td>A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Pediatric Patients &lt;12</td>
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<td>Sanofi</td>
<td>rFVIIIFc-XTEN</td>
<td>Phase 2</td>
<td>FVIII</td>
<td>A Phase 1/2a, Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Previously Treated Adults With Severe Hemophilia A</td>
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<td>rFVIIIFc-XTEN</td>
<td>Phase 1 Phase 2</td>
<td>FVIII</td>
<td>A Phase 1, Open-Label, Single-Site, Safety, Tolerability, and Pharmacokinetics Study of Repeat Doses of BIVV001</td>
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<td>MOD-5014</td>
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<td>Phase 1</td>
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<td>A Phase 1/Randomized, Single-blind, Placebo-controlled, Single Dose, Dose-escalated Study to Assess the Safety, Pharmacokinetic and Pharmacodynamic Profile of Subcutaneous Administration of a Long-acting Recombinant Factor VIIa in Healthy Adult Males</td>
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### Novel: Investigational factor product • Rare

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<td>TAK-755</td>
<td>Takeda</td>
<td>Recombinant ADAMTS13</td>
<td>Phase 3b- recruiting</td>
<td>Congenital thrombotic thrombocytopenic purpura</td>
<td>A Study of TAK-755 in Participants With Congenital Thrombotic Thrombocytopenic Purpura</td>
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<td>SHP-655</td>
<td>Takeda</td>
<td>Recombinant ADAMTS13</td>
<td>Phase 1- recruiting</td>
<td>Sickle cell disease</td>
<td>A Study of SHP655 (rADAMTS13) in Sickle Cell Disease (RAISE)</td>
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<td>TAK-755</td>
<td>Takeda</td>
<td>Recombinant ADAMTS13</td>
<td>Phase 2- not recruiting</td>
<td>Immune-mediated thrombotic thrombocytopenic purpura</td>
<td>Study of rADAMTS-13 (SHP655) in the Treatment of Participants With Acquired Thrombotic Thrombocytopenic Purpura (aTTP) (SOAR-HI)</td>
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<td>BAX-930</td>
<td>Takeda</td>
<td>Recombinant ADAMTS13</td>
<td>Phase 3- recruiting</td>
<td>Congenital thrombotic thrombocytopenic purpura</td>
<td>A Study of BAX 930 in Children, Teenagers, and Adults Born With Thrombotic Thrombocytopenic Purpura (TTP)</td>
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## Novel: Non-factor product • Factor VIII

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<tr>
<td>concizumab</td>
<td>Novo Nordisk</td>
<td>Anti-TFPI</td>
<td>II - NCT03196284</td>
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<td>A Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Haemophilia A and B Patients With Inhibitors (explorer™)</td>
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<td>Mim8</td>
<td>Novo Nordisk</td>
<td>Coagulation factor VIII mimetic antibody</td>
<td>II - NCT04204408</td>
<td>Haemophilia A With or Without Inhibitors</td>
<td>Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Subcutaneous Doses of NNC0365-3769 (Mim8) in Healthy Subjects and in Subjects With Haemophilia A With or Without Factor VIII Inhibitors</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT04204408?term=mim8&amp;draw=2&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT04204408?term=mim8&amp;draw=2&amp;rank=1</a></td>
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<tr>
<td>marstacimab</td>
<td>Pfizer, Inc.</td>
<td>Antibody to Tissue Factor Pathway Inhibitor</td>
<td>Phase 3; recruiting</td>
<td>Males 12 to 74 year of age with diagnosis of severe hemophilia A or moderately severe to severe hemophilia B with a minimum weight of 35kg at screening; participants will be assigned to treatment with PF-06741086 after a 6 month observation phase on their</td>
<td>An open-label study in adolescent and adult severe (coagulation factor activity &lt;1%) hemophilia A participants with or without inhibitors or moderately severe to severe hemophilia B participants (coagulation factor activity &lt;2%) with or without inhibitors</td>
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<td>Antibody to Tissue Factor Pathway Inhibitor</td>
<td>Phase 3; recruiting</td>
<td>Males 12 to 74 years of age with a diagnosis of severe hemophilia A or moderately severe to severe hemophilia B who successfully completed participation in B7841005</td>
<td>An open-label extension study to evaluate the long-term safety, tolerability, and efficacy of marstacimab prophylaxis in participants with severe hemophilia A and B with or without inhibitors</td>
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<tr>
<td>Fitusiran/ SAR439774</td>
<td>Sanofi</td>
<td>RNAI</td>
<td>Phase 3</td>
<td>Hem A and Hem B without inhibitor, who were previously under factor on demand treatment</td>
<td>ATLAS-A/B: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients With Hemophilia A or B, Without Inhibitory Antibodies to Factor VIII or IX</td>
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<td>Hem A and Hem B with or without inhibitor, who were previously under factor or BPA prophylactic treatment</td>
<td>A Study of Fitusiran in Severe Hemophilia A and B Patients Previously Receiving Factor or Bypassing Agent Prophylaxis (ATLAS-PPX)</td>
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<td>Sanofi</td>
<td>RNAI</td>
<td>Phase 3</td>
<td>Hem A and Hem B with inhibitor, who were previously under BPA on demand treatment</td>
<td>ATLAS-INH: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients with Hemophilia A or B, with Inhibitory Antibodies to Factor VIII or IX</td>
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<td>RNAI</td>
<td>Phase 3</td>
<td>Hem A and Hem B with or without inhibitor, who completed Phase 3 studies</td>
<td>Long-term Safety and Efficacy Study of Fitusiran in Patients With Hemophilia A or B, With or Without Inhibitory Antibodies to Factor VIII or IX (ATLAS-OLE)</td>
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<td>RNAI</td>
<td>Phase 2/3</td>
<td>Hem A and Hem B with inhibitor, pediatric patients 1-11 years of age</td>
<td>Fitusiran Prophylaxis in Male Pediatric Subjects Aged 1 to Less Than 12 Years With Hemophilia A or B (ATLAS-PEDS)</td>
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<td>Fitusiran/ SAR439774</td>
<td>Sanofi</td>
<td>RNAI</td>
<td>Phase 1 Phase 2</td>
<td>Hem A and Hem B with or without inhibitor, who completed Phase 1 study</td>
<td>An Open-label Extension Study of an Investigational Drug, Fitusiran, in Patients With Moderate or Severe Hemophilia A or B</td>
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<td>Fitusiran/ SAR439774</td>
<td>Sanofi</td>
<td>RNAI</td>
<td>Phase 1</td>
<td>Hem A and Hem B with or without inhibitor</td>
<td>A Phase 1 Single-ascending and Multi-ascending Dose, Safety, Tolerability and Pharmacokinetics Study of Subcutaneously Administered ALN-AT3SC in Healthy Adult Volunteers and Hemophilia A or B Patients (Moderate or Severe Hemophilia)</td>
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<tr>
<td>SIG-001</td>
<td>Sigilon Therapeutics, Inc</td>
<td>non-viral engineered cell based therapy</td>
<td>On Clinical Hold</td>
<td>FVIII</td>
<td>A Phase 1/2 Open-Label, Dose-Escalation, Safety, Tolerability, and Efficacy Study of SIG-001 in Adult Patients With Severe or Moderately-Severe Hemophilia A Without Inhibitors (SIG-001-121)</td>
<td>Novel therapeutic modality consisting of genetically modified allogeneic cells encapsulated in small molecule modified alginate spheres designed to avoid immune rejection by the host organism.</td>
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<tr>
<td>TRM-201 (rofecoxib)</td>
<td>Tremeau Pharmaceuticals, Inc</td>
<td>CDX-2 selective NSAID</td>
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<td>Hemophilic arthropathy, Patients with hemophilia A or B and a diagnosis of hemophilic arthropathy in one or more joints.</td>
<td>Rofecoxib Efficacy and Safety Evaluation Trial in Hemophilic Arthropathy (RESET-HA)</td>
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<td>marstacimab</td>
<td>Pfizer, Inc. Antibody to Tissue Factor Pathway Inhibitor</td>
<td>Phase 3; recruiting</td>
<td>Males 12 to 74 year of age with diagnosis of severe hemophilia A or moderately severe to severe hemophilia B with a minimum weight of 35kg at screening; participants will be assigned to treatment with PF-06741086 after a 6 month observation phase on their</td>
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<td>Fitusiran/</td>
<td>Sanofi RNAi</td>
<td>Phase 3</td>
<td>Hem A and Hem B without inhibitor, who were previously under factor on demand treatment</td>
<td>ATLAS-A/B: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients With Hemophilia A or B, Without Inhibitory Antibodies to Factor VIII or IX</td>
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<td>SAR439774</td>
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<td>HEM A AND HEM B WITHOUT INHIBITOR, WHO WERE PREVIOUSLY UNDER FACTOR ON DEMAND TREATMENT</td>
<td>ATLAS-INH: A Phase 3 Study to Evaluate the Efficacy and Safety of Fitusiran in Patients with Hemophilia A or B, With Inhibitory Antibodies to Factor VIII or IX</td>
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**Recombinant Clotting Factor • Factor VIII**

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<td>HEMA Biologics</td>
<td>Coagulation VIIa, Recombinant, non-biosimilar</td>
<td>Phase 3b - Finalizing CSR</td>
<td>Treatment of bleeding, Congenital VIII or IX with inhibitors: birth to &lt;12 years</td>
<td>PERSEPT 2 --NCT02448680 - A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from birth to &lt;12 years old with Inhibitors to Factor VIII or IX</td>
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<tr>
<td>Coagulation FVIIa (Recombinant) Eptacog Beta or LR769</td>
<td>HEMA Biologics</td>
<td>Coagulation VIIa, Recombinant, non-biosimilar</td>
<td>Phase 3 - Finalizing CSR</td>
<td>Prevention of excessive bleeding, Congenital VIII or IX with inhibitors: elective surgery or other invasive procedures</td>
<td>PERSEPT 3 --NCT02548143 - A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients With Inhibitors to Factor VIII or IX Undergoing Elective Surgery</td>
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<tr>
<td>Coagulation FVIIa (Recombinant) Eptacog Beta or LR769</td>
<td>HEMA Biologics</td>
<td>Coagulation VIIa, Recombinant, non-biosimilar</td>
<td>Phase 1b - Open access published link: <a href="https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.13357">https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.13357</a></td>
<td>Dose Ranging Study for VIII or IX with inhibitors: ? 12 years</td>
<td>Dose-Ranging Study (N=15) - Phase 1b - Study Design Dose escalation, pharmacokinetics, safety and in vivo pharmacodynamics Ducore, et al 2017 NCT01708564</td>
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<td>SCT800</td>
<td>Sinocelltech Ltd.</td>
<td>Recombinant VIII</td>
<td>Phase 4</td>
<td>Moderate to Severe VIII</td>
<td>A Multicenter, Open, Extension Trial to Evaluate Safety and Efficacy of Recombinant Human Coagulation Factor VIII (SCT800) During Long Term Treatment in Previously Treated Patients With Severe Haemophilia A.</td>
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<td>SCT800</td>
<td>Sinocelltech Ltd.</td>
<td>Recombinant VIII</td>
<td>Phase 3</td>
<td>Severe VIII</td>
<td>A Multicenter Phase III Uncontrolled Open-label Trial to Evaluate Safety and Efficacy and Pharmacokinetics of Recombinant Human Coagulation Factor VIII (SCT800) in Previously Treated Paediatric Patients With Severe Haemophilia A.</td>
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<td>INDICATION DETAILS</td>
<td>OFFICIAL STUDY TITLE</td>
<td>CLINICAL TRIAL NOTES</td>
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<td>Dalcinonacog alfa (CB 2679d/ISU304)</td>
<td>Catalyst Biosciences</td>
<td>Recombinant IX</td>
<td>Phase 1/2</td>
<td>IX</td>
<td>A Phase I, Open-label, Multi-center, Dose-escalation Study to Investigate the Safety, Pharmacokinetics and Pharmacodynamics of ISU304 in Previously Treated Hemophilia B Patients</td>
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<td>HEMA Biologics</td>
<td>Coagulation VIIa, Recombinant, non-biosimilar</td>
<td>Phase 3b - Finalizing CSR</td>
<td>Treatment of bleeding, Congenital VIII or IX with inhibitors: birth to &lt;12 years</td>
<td>PERSEPT 2 --NCT02448680 - A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from birth to &lt;12 years old with Inhibitors to Factor VIII or IX</td>
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<td>Phase 3 - Finalizing CSR</td>
<td>Prevention of excessive bleeding, Congenital VIII or IX with inhibitors: elective surgery or other invasive procedures</td>
<td>PERSEPT 3 --NCT02548143 - A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients With Inhibitors to Factor VIII or IX Undergoing Elective Surgery</td>
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Clinical Studies: How Do They Work?

BY HFA STAFF WITH SOURCING FROM THE NATIONAL INSTITUTES OF HEALTH’S NATIONAL LIBRARY OF MEDICINE

A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials (also called interventional studies) and observational studies. In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants’ behavior, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients or to no intervention. Some clinical trials compare interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful or no different than available alternatives (including no intervention). The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants. Clinical trials used in drug development are often described by phase. These phases are defined by the Food and Drug Administration (FDA).

In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions (which can include medical products such as drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial). For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health. Investigators assess health outcomes in groups of participants who receive interventions, but participants are not assigned to specific interventions by the investigator as they would be in a clinical trial.

WHO CONDUCTS?
Every clinical study is led by a principal investigator, who is often a medical doctor. Clinical studies also have a research team that may include doctors, nurses, social workers and other health care professionals. Clinical studies can be sponsored, or funded, by pharmaceutical companies, academic medical centers, voluntary groups and other organizations, in addition to federal agencies. Doctors, other health care providers and other individuals can also sponsor clinical research.

WHO PARTICIPATES?
Some studies seek participants who have the illnesses or conditions that will be studied, while other studies are looking for healthy participants. Some studies are limited to a predetermined group of people who are asked by researchers to enroll.

WHO’S ELIGIBLE?
The factors that allow someone to participate in a clinical study are called inclusion criteria. The factors that disqualify someone from participating are called exclusion criteria. Criteria are listed in the study protocol. Factors are based on characteristics such as age, gender, the type and stage of a disease, previous treatment history and other medical conditions.

WHERE?
Studies take place in hospitals, universities, doctors’ offices and community clinics, depending on who is conducting the study.

LENGTH?
The length of a clinical study varies, depending on what is being studied. Participants are told how long the study will last before they enroll.

PROTECTIONS?
Informed consent is a process used by researchers to provide potential and enrolled participants with information about a clinical study. It protects participants and provides enough information for a person to understand the risks of potential benefits of and alternatives to the study. (See page 6 for more information on informed consent.)

Institutional Review Boards
Each federally supported or conducted clinical study and each study of a drug, biological product or medical device regulated by the FDA must be reviewed, approved and monitored by an Institutional Review Board (IRB). An IRB is made up of doctors, researchers and members of the community who make sure the study is ethical and the rights and welfare of participants are protected.

Relationship to Usual Health Care
While enrolled in a clinical study, participants continue to see their usual health care providers, who work with the research team to make sure the study will not conflict with other medications or treatments.
The Five Phases of A Clinical Trial

**The Five Phases of A Clinical Trial**

**Early Phase**
(Formerly listed as Phase 0)

**Exploratory study involving very limited human exposure to the drug, with no therapeutic or diagnostic goals. Examples would include screening studies and microdose studies.**

**Phase 1**

**Studies that are usually conducted with healthy volunteers and that emphasize safety. The goal is to find out what the drug’s most frequent and serious adverse events are and, often, how the drug is metabolized and excreted.**

**Phase 2**

**Studies that gather preliminary data on effectiveness, as in whether the drug works in people who have a certain disease or condition. For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance, called a placebo, or a different drug. Safety continues to be evaluated, and short-term adverse events are studied.**

**Phase 3**

**Studies that gather more information about safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs.**

**Phase 4**

**Studies occurring after the FDA has approved a drug for marketing. These include post-market requirement and commitment studies that are required of, or agreed to by, the study sponsor. These studies gather additional information about a drug’s safety, efficacy or optimal use.**

**IMPORTANT FACTS ABOUT ELOCTATE® [ANTIHEMOPHILIC FACTOR (RECOMBINANT), FC FUSION PROTEIN]**

Please read this information carefully before using ELOCTATE and each time you get a refill, as there may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**WHAT IS ELOCTATE?**

- ELOCTATE is an injectable medicine that is used to help control and prevent bleeding in people with Hemophilia A (congenital Factor VIII deficiency).
- Your healthcare provider may give you ELOCTATE when you have surgery.

**WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ELOCTATE?**

- You should not use ELOCTATE if you are allergic to ELOCTATE or any of its other ingredients. Tell your healthcare provider if you have had an allergic reaction to any Factor VIII product prior to using ELOCTATE.
- You can have an allergic reaction to ELOCTATE. Call your healthcare provider or emergency department right away if you have any of the following symptoms: difficulty breathing, chest tightness, swelling of the face, rash or hives.
- Your body may also make antibodies called “inhibitors” against ELOCTATE. This can stop ELOCTATE from working properly.
- Your healthcare provider may give you blood tests to check for inhibitors.
- If you have risk factors for developing abnormal blood clots in your body, such as an indwelling venous catheter, treatment with Factor VIII may increase this risk.

**THE MOST COMMON SIDE EFFECTS OF ELOCTATE INCLUDE: joint pain, general discomfort, muscle pain, headache, and rash, in previously treated patients, and Factor VIII inhibition, device-related blood clotting, and rash in previously untreated patients.**

**WHAT SHOULD I TELL MY HEALTHCARE PROVIDER BEFORE STARTING ELOCTATE?**

Tell your healthcare provider about all your health conditions, including if you:

- Have or have had any medical problems.
- Are taking any prescription and non-prescription medicines, including over-the-counter medicines, supplements, or herbal medicines.
- Are pregnant or planning to become pregnant. It is not known if ELOCTATE may harm your unborn baby.
- Are breastfeeding. It is not known if ELOCTATE passes into breast milk and if it can harm your baby.

**AFTER STARTING ELOCTATE:**

- If your bleeding is not controlled and you experience a lack of clinical response to Factor VIII therapy, call your healthcare provider right away.
- Medicines are sometimes prescribed for purposes other than those listed here. Do not use ELOCTATE for a condition for which it was not prescribed. Do not share ELOCTATE with other people, even if they have the same symptoms that you have.

**HOW SHOULD I USE ELOCTATE?**

ELOCTATE should be administered as ordered by your healthcare provider. You should be trained on how to do infusions by your healthcare provider. Many people with hemophilia A learn to infuse ELOCTATE by themselves or with the help of a family member. See the booklet called “Instructions for Use” packaged in your ELOCTATE for directions on infusing. If you are unsure of the procedure, please ask your healthcare provider.

**QUESTIONS?**

The risk information provided here is not comprehensive. To learn more, talk about ELOCTATE with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at www.eloctate.com or 1-855-MyELOCTATE (693-5628). You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

**MANUFACTURED BY:**

Bioverativ Therapeutics Inc.
Waltham, MA 02451 USA

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**INTERESTED IN PARTICIPATING?**

Anyone interested in participating in a clinical study should know as much as possible about the study and feel comfortable asking the research team questions about the study, the related procedures and any expenses. The following questions may be helpful during such a discussion:

- What is being studied and how long will it last?
- Why do researchers believe the intervention being tested might be effective?
- What will I have to do and is hospitalization required?
- Who will know which intervention I receive during the trial? Will I know? Will members of the research team know?
- How do the possible risks, side effects and benefits of this trial compare with those of my current treatment?
- What tests and procedures are involved?
- Who will pay for my participation and will I be reimbursed for other expenses?
- What type of long-term follow-up care is part of this trial?
- If I benefit from the intervention, will I be allowed to continue receiving it after the trial ends?
- Will results of the study be provided to me? Who will oversee my medical care while I am participating in the trial?
- What happens if I am injured during the study?

**WHAT HAPPENS IF I AM INJURED DURING THE STUDY?**

- If you are injured during a study, you should promptly contact your study physician. Additional information may be required to determine if you are still eligible to participate in the study.
- You should receive the best medical care for your condition.
- You should be reimbursed for other expenses.

**WILL RESULTS OF THE STUDY BE PROVIDED TO ME? WHO ELSE CAN SEE THE RESULTS?**

- If you have questions about whether you will be able to see the results of the study, you should contact your research team.
- It is possible that other researchers may use the results of the study to advance medical knowledge. For example, the results of your study may be used to improve a current treatment or to test new treatments.

**IF I BENEFIT FROM THE INTERVENTION, WILL I BE ALLOWED TO CONTINUE RECEIVING IT AFTER THE TRIAL ENDS?**

- It depends on the study and the intervention. Contact your research team for more information.

**WHAT IS BEING STUDIED AND HOW LONG WILL IT LAST?**

- The Five Phases

**THE FIVE PHASES**

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**ANYONE INTERESTED IN PARTICIPATING?**

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