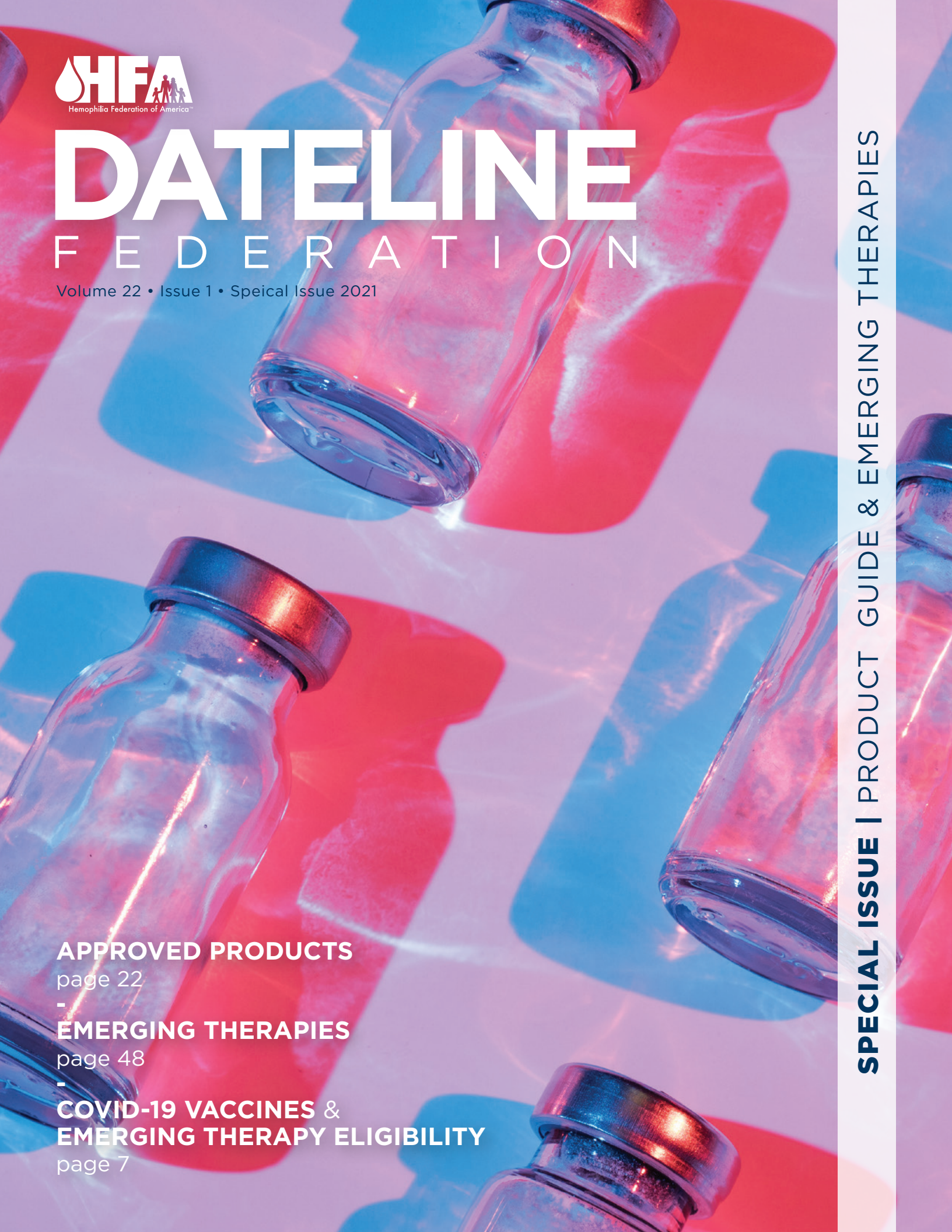

Hemophilia Federation of America

DATELINE FEDERATION

Volume 22 • Issue 1 • Speical Issue 2021

SPECIAL ISSUE | PRODUCT GUIDE & EMERGING THERAPIES

HFA
Hemophilia Federation of America™

Assisting, educating, and advocating for the bleeding disorders community since 1994.

Volume 22 • Issue 1 • Special Issue 2021

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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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DEAR FRIENDS—

One of our guiding principles since our founding has been to provide the tools and education patients and their families need to make informed decisions about their bleeding disorder. This annual special edition of *Dateline Federation* is a product of our focus on that principle. We hope you find this tool helpful in your journey navigating treatment options and emerging therapies and a conversation starter for you and your medical providers.

It was 17 years ago when I was choosing a treatment option for my newborn son with severe hemophilia A. The overwhelming feeling remains vivid. It was a confusing and scary process, despite having wonderful support from the staff at our local Hemophilia Treatment Center. I was a mom, unsure of how to even spell hemophilia at that point, just wanting to make the right call for my baby's health. But, I didn't know what questions to ask, what specifics to consider or even what our options were. At that time, little did I know that the number of treatment options for bleeding disorders would nearly double before my son even graduated high school and that novel treatment options beyond a recombinant clotting factor would become readily accessible.

As patients, we have the *right* to know our options. But it is our *responsibility* to educate and empower ourselves about our disorder. From our community's history we know that patients and their families look to advocacy organizations such as HFA to provide the facts and information needed. HFA remains committed to being a trusted source of information for you. Furthermore, we are steadfast in our commitment to ensure a safe blood supply and transparency around treatment options and their efficacy.

We're continually evaluating the educational content we produce, always looking for ways to improve the resources we create for families. This product guide and list of emerging therapies has evolved over the past five years in an effort to create a tool that is useful. Our team is currently exploring ways to dive deeper into the topics you see in these pages, including an overview of products by disorder, access issues in insurance coverage and a look at the future of gene therapy and other new novel treatments.

As always, we want to hear from you to know if these are topics you want us to focus on, with the possibility of HFA hosting a multi-day online event focused on treatment options. What do you think is missing from the current tools and resources available to you and your family around treatment options and emerging therapies? Who do you want to hear from: doctors, researchers, manufacturers? Contact us at info@hemophiliafed.org; we'd love to hear from you!

Our legacy as a community of informed, engaged, educated and empowered advocates demands we always continue to gain the knowledge we need to move forward toward improved treatments and outcomes for everyone. Let this resource be a launching point for you.

Sonji Wilkes

Sonji Wilkes

Hemophilia Mom
VP, Policy & Advocacy

esperoct®

antihemophilic factor (recombinant), glycopegylated-exei

Brief Summary information about ESPEROCT® [antihemophilic Factor (recombinant), glycopegylated-exei]

This information is not comprehensive.

- Talk to your healthcare provider or pharmacist
- Visit www.novo-pi.com/esperoct.pdf to obtain FDA-approved product labeling
- Call 1-800-727-6500

Patient Information

ESPEROCT®
[antihemophilic factor (recombinant), glycopegylated-exei]

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 regarding the dose and schedule for infusing ESPEROCT® so that your treatment will work best for you.

What is ESPEROCT®?

ESPEROCT® is an injectable medicine used to replace clotting Factor VIII that is missing in patients with hemophilia A. Hemophilia A is an inherited bleeding disorder in all age groups that prevents blood from clotting normally.

ESPEROCT® is used to treat and prevent or reduce the number of bleeding episodes in people with hemophilia A.

Your healthcare provider may give you ESPEROCT® when you have surgery.

Who should not use ESPEROCT®?

You should not use ESPEROCT® if you

- are allergic to Factor VIII or any of the other ingredients of ESPEROCT®
- if you are allergic to hamster proteins

If you are not sure, talk to your healthcare provider before using this medicine.

Tell your healthcare provider if you are pregnant or nursing because ESPEROCT® might not be right for you.

What should I tell my healthcare provider before I use ESPEROCT®?

You should tell your healthcare provider if you:

- Have or have had any medical conditions.
- Take any medicines, including non-prescription medicines and dietary supplements.
- Are nursing.
- Are pregnant or planning to become pregnant.
- Have been told that you have inhibitors to Factor VIII.

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.

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 learn 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. This should be checked by your healthcare provider. 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®

If you forget a dose, 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 infusions as scheduled and continue as advised by your healthcare provider.

If you stop using ESPEROCT®

Do not stop using ESPEROCT® without consulting your healthcare provider.

If you have any further questions on the use of this product, ask your healthcare provider.

What if I take too much ESPEROCT®?

Always take ESPEROCT® exactly as your healthcare provider has told you. You should check with your healthcare provider if you are not sure. If you infuse more ESPEROCT® than recommended, tell your healthcare provider as soon as possible.

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 coagulation Factor VIII products. **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, dizziness, difficulty breathing, and/or swelling of the face.

Your body can also make antibodies called "inhibitors" against ESPEROCT®, which may stop ESPEROCT® from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.

These are not all of the possible side effects from ESPEROCT®. Ask your healthcare provider for more information. You are encouraged to report side effects to FDA at 1-800-FDA-1088.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

What are the ESPEROCT® dosage strengths?

ESPEROCT® comes in five different dosage strengths. The actual number of international units (IU) of Factor VIII in the vial will be imprinted on the label and on the box. The five different strengths are as follows:

Cap Color Indicator	Nominal Strength
Red	500 IU per vial
Green	1000 IU per vial
Gray	1500 IU per vial
Yellow	2000 IU per vial
Black	3000 IU per vial

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider.

How should I store ESPEROCT®?

Prior to Reconstitution (mixing the dry powder in the vial with the diluent):

Protect from light. Do not freeze ESPEROCT®.

ESPEROCT® can be stored in refrigeration at 36°F to 46°F (2°C to 8°C) for up to 30 months until the expiration date stated on the label. During the 30 month shelf life, ESPEROCT® may be kept at room temperature (not to exceed 86°F/30°C) for up to 12 months, **or** up to 104°F (40°C) for no longer than 3 months.

If you choose to store ESPEROCT® at room temperature:

- Record the date when the product was removed from the refrigerator.
- Do not return the product to the refrigerator.
- Do not use after 12 months if stored up to 86°F (30°C) **or** after 3 months if stored up to 104°F (40°C) **or** the expiration date listed on the vial, whichever is earlier.

Do not use this medicine after the expiration date which is on the outer carton and the vial. The expiration date refers to the last day of that month.

After Reconstitution:

The reconstituted (the final product once the powder is mixed with the diluent) ESPEROCT® should appear clear and colorless without visible particles.

The reconstituted ESPEROCT® should be used immediately.

If you cannot use the reconstituted ESPEROCT® immediately, it must be used within 4 hours when stored at or below 86ºF (30°C) or within 24 hours when stored in a refrigerator at 36°F to 46°F (2°C to 8°C). Store the reconstituted product in the vial.

Keep this medicine out of the sight and out of reach of children.

What else should I know about ESPEROCT® and hemophilia A?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use ESPEROCT® for a condition for which it is not prescribed. Do not share ESPEROCT® with other people, even if they have the same symptoms that you have.

Revised: 10/2019

ESPEROCT® is a trademark of Novo Nordisk Health Care AG.

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

More detailed information is available upon request. Available by prescription only.

Manufactured by:
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

For information about ESPEROCT® contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536, USA
1-800-727-6500

US19ESP00168 December 2019

novo nordisk®

COVID-19 VACCINES DON'T STOP EMERGING THERAPY OPTIONS FOR THOSE WITH BLEEDING DISORDERS

BY HFA STAFF WITH SCIENTIFIC REVIEW
BY DR. DAVID CLARK AND DR. LISA HENSLEY

Many people have questions about the COVID-19 vaccines. This article will answer one primary question: **Can getting vaccinated for COVID-19 cut off treatment options for emerging bleeding disorder treatments and therapies?** Of the three vaccines currently available in the United States, the Pfizer and Moderna vaccines use messenger ribonucleic acid (mRNA) technology while the Johnson & Johnson vaccine uses a viral vector.

HOW THESE VACCINES WORK

The virus that causes COVID-19 is called SARS-CoV-2, which is a coronavirus. Coronaviruses have protein spikes sticking out of them that allow the virus to attach to and enter cells. All three vaccines use that spike protein to help our bodies develop an immune response to prevent illness.

In the case of the mRNA vaccines, when you get the shot, mRNA goes into cells and sends "instructions" to the cells to create the spike protein. By itself, the spike protein will not cause COVID-19 — it's just one piece of the virus. The mRNA lasts in your system for about 24 hours and then starts to degrade, but your cells will continue to express the spike proteins for a few days. Your immune system recognizes those spike proteins as foreign and starts creating an immune response against them. The first dose of the vaccine starts this process and provides some protection. The second dose raises and refines that protection to about 95% and helps the effects of the vaccine last longer. The refinement is like the second time you play an opponent in a sport: Even if they change some of their strategy, you are better able to handle them.

The Johnson & Johnson vaccine works differently, using something called a "viral vector." A viral vector is created when scientists take a nonpathogenic virus (that doesn't make humans sick) and alter it to do something different. For the vaccine, Johnson & Johnson took an adenovirus and replaced part of its genetic instructions with the genes to create the SARS-CoV-2 spike protein. When you get the shot, the adenovirus enters your cells, giving them the genetic instructions to make the spike protein. Once those spike proteins start appearing on the surfaces of your cells, your immune system recognizes them as foreign and builds an immune response against them. As with the mRNA, the viral vector with the DNA in it only lasts a short time. This is because the viral vector does not replicate well, so it also degrades out of the body. The Johnson & Johnson vaccine requires only one dose at this time.

COMPARED TO GENE THERAPY

While the process is similar to what you have heard about gene therapy for hemophilia, it is significantly different in the sense that it uses a completely different viral vector and therefore would not interfere with you having access to gene therapy in the future. Other parameters in your health profile might keep you from getting gene therapy for hemophilia, but it won't be because you had the vaccine.

The Johnson & Johnson vaccine uses an **adenovirus**, which is altered to create the protein spike. Gene therapy being studied for hemophilia treatment uses an **adeno-associated virus (AAV)**. Even though they sound the same, these two types of viruses are different and are not related, and having a Johnson & Johnson adenovirus vaccine will not cause you to create antibodies to an AAV.

SO, LET'S BUST SOME MYTHS:

MYTH 1

Getting an mRNA vaccine will prevent you from being able to receive future bleeding disorder treatments that use mRNA.

There is no evidence that having an mRNA vaccine will close off access to future bleeding disorder treatments that use mRNA. The mRNA from the vaccine goes in and gives instructions to make the SARS-CoV-2 spike protein and then is degraded in about 24 hours.

MYTH 2

Getting a viral vector vaccine will prevent you from being able to receive future bleeding disorder gene therapy treatments.

There is no evidence that having a gene therapy vaccine made from an adenovirus will close off access to future gene therapy bleeding disorder treatments that use AAV.

MYTH 3

Getting an mRNA vaccine will change your DNA.

Getting an mRNA vaccine does not create any permanent genetic changes. mRNA is a piece of genetic code that goes in, gives instructions to your cells, and, in the case of the vaccine mRNA, starts leaving your system in about 24 hours. It's generally gone in about three days. In addition, the vaccine mRNA works on the outer part of muscle cells without going into the cells' nuclei, which is where your genes/DNA are located.

MYTH 4

The vaccines can give you COVID-19.

Because the vaccines only use the SARS-CoV-2 spike protein, there is no way to get COVID-19 from a vaccine.

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 7 years old are asked to assent to participate in research studies.

FDA REGULATIONS

Under the U.S. Food and Drug Administration regulations, an Institutional Review Board 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

We cannot emphasize enough that participants, sometimes referred to as human subjects in a clinical research setting, should ask questions about their participation in a clinical trial or research study prior to signing up. Here are questions you should ask about a clinical trial or research study and the information you should glean from asking:

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.
- 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 FDA'S GENE AND CELL THERAPY FRAMEWORK

and its Impact on New Hemophilia Treatments in 2021 and Beyond

BY ANGELA N. JOHNSON, PH.D., RAC, CPGP
SENIOR DIRECTOR OF REGULATORY AFFAIRS AT SIGILON THERAPEUTICS IN CAMBRIDGE, MASSACHUSETTS, AND REGULATORY STRATEGY LECTURER AT NORTHEASTERN UNIVERSITY IN BOSTON

More cell and gene therapy products are being developed and entering clinical trials each year. The U.S. Food and Drug Administration plays a key role in overseeing drug development, including providing guidance and receiving investigational new drug applications or requests to start a new clinical trial submitted by drug developers.

In 2021, there are more than 1,000 cell and gene therapy clinical trials, including more than a dozen in hemophilia. FDA announced it expects more than 200 new requests to start clinical trials based on gene and cell technologies each year. By 2025, FDA expects 10 to 20 new CGT treatments will be approved annually.

Gene therapy treatments for hemophilia have shown potential to eliminate the need for prophylactic factor infusions and injections. Unlike gene therapy, newer technologies such as genetically modified factor-producing cells do not involve changes in patient genetic material and may allow better control of dosing as well as redosing. But many challenges and uncertainties face researchers and drug developers. To help set best practices across the industry, FDA guidance frameworks play an important role in safe and efficient development of CGT products.

WHAT ARE FDA GUIDANCE FRAMEWORKS?

To help the companies developing new drugs, FDA publishes recommendations called guidance documents. Unlike the laws passed by Congress or formal regulations, guidance documents contain FDA expectations and current scientific thinking not required by law. If we think of regulations as what the law requires drug developers to do, we can think of guidance documents as a playbook of how to do it in most, but not all, cases.

Guidance frameworks are groups of related guidance documents, such as those relating to CGT. New guidance creation is an important part of FDA's ongoing mission to expedite innovations that make medical products more effective, safer and more affordable. Guidance documents are written and published according to a process called Good Guidance Practice, which describes how FDA staff will bring together expert and public feedback in guidance recommendations.

GROWING EXPECTATIONS FOR CGT IN HEMOPHILIA

FDA's first draft guidance document dedicated to early development of CGT clinical trials — Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products — was released as a draft in 2013 and finalized in 2015. It discussed many recommendations for manufacturing, testing and patient safety and follow-up.

In 2016, Congress passed the 21st Century Cures Act or Cures Act, which includes provisions designed to expedite and streamline development of innovative new medicines. This law builds on FDA's existing responsibilities and established regenerative medicine therapies, including gene therapy, cell therapy, products made from tissues and combinations of these products. FDA published guidance in 2017 and updated in 2020 to help industry apply these new regulations that together are referred to as the FDA regenerative medicine framework. Both human gene editing and transfer, as well as genetically modified cells that lead to a sustained factor production in hemophilia, are considered to be regenerative medicine therapies by FDA.

Guidance for developing CGT products specifically for hemophilia was published by FDA in 2018. Then in 2020, it was updated when FDA launched its expanded framework for cell and gene therapies. This framework contained several new guidance documents, including hemophilia CGT. This brought the total number of guidance documents in the framework to 27. In 2021, we can see how the evolution of hemophilia gene and cell therapy has been affected by the development of this framework.

EARLY 2020: FDA LAUNCHES CELL AND GENE THERAPY GUIDANCE FRAMEWORK

On Jan. 28, 2020, FDA launched its landmark guidance framework for CGT products. Updates included improvements to the guidance for hemophilia and

CONTINUED ON PAGE 17

GUIDANCE, REGULATION AND LAWS THAT MAKE UP THE U.S. FDA FRAMEWORK FOR DEVELOPING NEW CELL AND GENE THERAPY (CGT) PRODUCTS FOR HEMOPHILIA

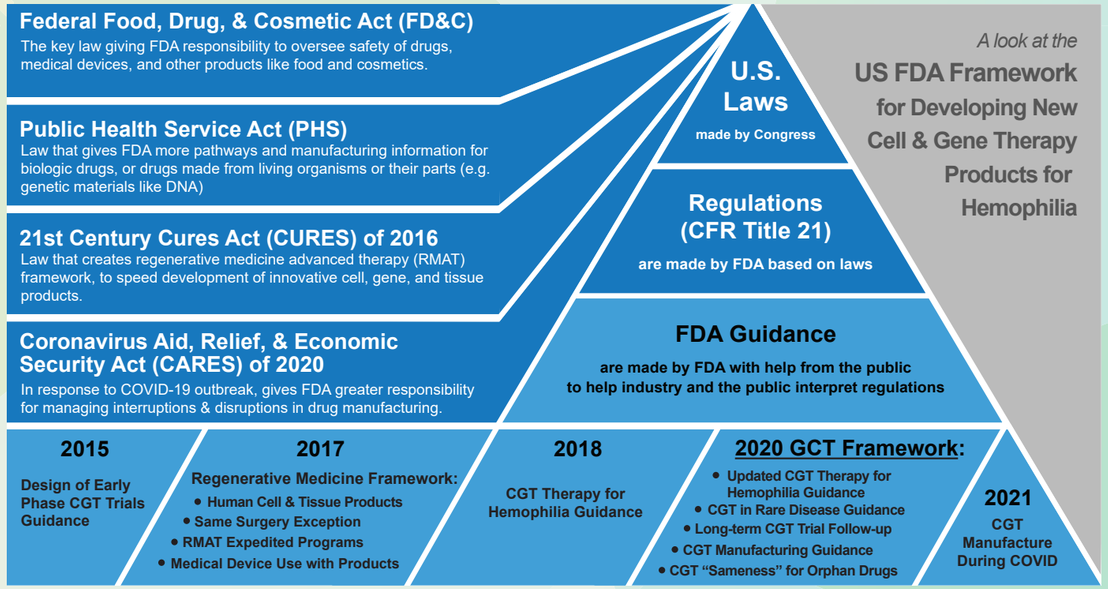


Image Source: Adapted for Sigilon Therapeutics, Inc. with permission of the author.

For the treatment of bleeding episodes in people* with hemophilia A or B with inhibitors

I'M READY TO MOVE ON

Get rapid, predictable, and reliable bleed control with SEVENFACT 225†

Rapid effect: 3 hour

At 3 hours, 84% of mild/moderate bleeding episodes were controlled with a single dose

Predictable‡ response: 84%

At 9 hours, 84% of mild/moderate bleeding episodes treated achieved bleed control after a single dose

Reliable control: 99.5%

At 24 hours, 99.5% of mild/moderate bleeding episodes were resolved

Convenient home use: 98%

98% of bleeding episodes were treated at home

† 225 mcg/kg initial dosing regimen in the clinical trial.

‡ As seen in the clinical trial.

Summary of Selected Safety Information

What is the most important information I should know about SEVENFACT?

The most serious possible side effect of SEVENFACT is abnormal clotting involving blockage of blood vessels, which include stroke, blockage of the main blood vessel to the lung, and deep vein blood clots.

You should know the signs of abnormal clotting and seek medical help immediately if they occur. Signs of clotting in places other than your site of bleeding can include new onset of swelling and pain in limbs, new onset of chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness or speech.

*What is SEVENFACT?

SEVENFACT is an injectable medicine used for the treatment and control of bleeding episodes occurring in adults and adolescents 12 years of age and older with Hemophilia A or B with inhibitors.

Injecting medicines requires special training; do not attempt to self-infuse unless you have been taught how by your healthcare provider.

Who should not use SEVENFACT (coagulation factor VIIa)?

You should not use SEVENFACT if you are allergic to rabbits, or if you have known allergies to SEVENFACT or any of its components. Seek immediate medical help if you experience hives, itching, rash, difficulty breathing with cough or wheezing, swelling around the mouth and throat, tightness of the chest, dizziness or fainting, or low blood pressure after taking SEVENFACT.

Tell your healthcare provider prior to using SEVENFACT if you have begun treatment of a bleeding episode with another bypassing agent.

What should I tell my healthcare provider before I use SEVENFACT?

Tell your healthcare provider if you are pregnant, are nursing, or plan to become pregnant; if you have had prior blood clots, heart disease or heart failure, abnormal heart rhythms, prior pulmonary clots, or heart surgery; or if you have or have had any other medical conditions.

What are the possible side effects of SEVENFACT?

The most common adverse reactions for SEVENFACT are headache, dizziness, infusion-site discomfort, infusion-site hematoma, and infusion-related reaction and fever.

Seek immediate medical help if you have signs of a blood clot or an allergic reaction.

To report SUSPECTED ADVERSE REACTIONS or product complaints, contact HEMA Biologics at 1-855-718-4362. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Patient Product Information on the next page.

NEW

SevenFACT®

Coagulation Factor VIIa (Recombinant)-jncw

Make the move

PATIENT PRODUCT INFORMATION

SEVENFACT® (SEV-en-fact) coagulation factor VIIa (recombinant)-jncw

For Intravenous Injection After Reconstitution Only

PLEASE READ PATIENT PRODUCT INFORMATION AND THE INSTRUCTIONS FOR USE THAT COME WITH SEVENFACT BEFORE YOU START TAKING THIS MEDICINE AND EACH TIME YOU GET A REFILL. THERE MAY BE NEW INFORMATION.

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

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT SEVENFACT?

The most serious possible side effect of SEVENFACT is abnormal blood clotting involving blockage of blood vessels, which include stroke, blockage of the main blood vessel to the lung, and deep vein blood clots.

You should know the signs of abnormal clotting (thrombosis) described below and seek medical help immediately if they occur.

New onset of swelling and pain in the limbs or abdomen, new onset of chest pain, shortness of breath, loss of sensation or motor power, and altered consciousness or speech can all be signs of clot formation in places other than your site of bleeding. Seek immediate medical attention if you experience one or more of these symptoms.

SEVENFACT should be used as prescribed and directed by your healthcare provider.

WHAT IS SEVENFACT?

SEVENFACT is a recombinant human Factor VIIa protein for injection. SEVENFACT can allow adolescents and adults with Hemophilia A or B with inhibitors to create clotting at the site of bleeding without needing Coagulation Factor VIII or IX replacement.

SEVENFACT, coagulation factor VIIa (recombinant)-jncw, is indicated for the treatment and control of bleeding episodes occurring in adults and adolescents 12 years of age and older with Hemophilia A or B with inhibitors.

Injecting medications requires special training. Do not attempt to self-infuse unless you have been taught how by your health care provider or hemophilia treatment center. Once trained, you will need additional infusion materials along with your SEVENFACT so that you can successfully treat your bleeding episodes at home. Be sure to collect all necessary infusion materials before starting the reconstitution process.

SEVENFACT comes in a sterile dry powdered dosage form that must be reconstituted with sterile Water for Injection.

It is not known if SEVENFACT is safe and effective in children under 12 years of age.

WHO SHOULD NOT USE SEVENFACT?

You should not use SEVENFACT if you:

- Are allergic to rabbits.
- Have known allergies to SEVENFACT or any of its components.

Tell your doctor prior to infusing SEVENFACT if you have begun treatment of a bleeding episode with another bypassing agent such as activated prothrombin complex concentrate (FEIBA®).

WHAT SHOULD I TELL MY HEALTHCARE PROVIDER BEFORE I USE SEVENFACT?

Tell your healthcare provider if you:

- Are pregnant, planning to become pregnant or nursing, as SEVENFACT has not been studied in patients with Hemophilia A or B with inhibitors who are pregnant or nursing.
- Had prior blood clots, heart disease, heart failure, abnormal heart rhythms, prior pulmonary clots or heart surgery.
- Have or have had any other medical conditions.

You and your doctor can then decide whether SEVENFACT is the right treatment for you, as well as the proper timing and doses you will need for SEVENFACT to control your bleeding episodes at home.

HOW SHOULD I USE SEVENFACT?

Treatment with SEVENFACT should be started by a healthcare provider who is experienced in the care of patients with Hemophilia A or B with inhibitors.

SEVENFACT is given as an injection into your vein.

You may infuse SEVENFACT at a hemophilia treatment center, at your healthcare provider's office, or in your home. You should be trained on how to infuse by your healthcare provider or hemophilia treatment center. Many people with inhibitors learn to infuse by themselves or with the help of a family member.

Treating at first sign of a bleed is important for bleed management. Your healthcare provider will tell you how much

SEVENFACT to use based on your weight and when to administer SEVENFACT.

To administer SEVENFACT:

- Collect all materials needed for your prescribed dose
- Follow the **Instructions For Use** guide to reconstitute the prescribed number of SEVENFACT vials
- Infuse following your healthcare provider's instructions, using infusion materials from your pharmacy

CONTACT YOUR HEALTHCARE PROVIDER IF YOU:

- Miss a dose, or
- Administer more than your prescribed dose, or
- Think your bleed is not controlled within the expected time frame discussed with your healthcare provider.

WHAT SHOULD I AVOID WHILE USING SEVENFACT?

- Avoid activity that can create more bleeding once you have completed your SEVENFACT infusion
- Avoid mixing SEVENFACT with other medications
- Avoid infusing SEVENFACT and other factor-containing therapies [such as activated prothrombin complex concentrate (aPCC) or other recombinant Factor VIIa products] at the same time. This increases your risk of having a disabling blood clot.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF SEVENFACT?

The most common adverse reactions reported in clinical trials for SEVENFACT were headache, dizziness, infusionsite discomfort, infusion-site hematoma, infusion-related reaction and fever.

A serious allergic reaction to SEVENFACT may occur. If you experience the severe symptoms of an allergic reaction after infusing SEVENFACT, seek immediate medical attention. Severe symptoms occur when your immune system reacts very strongly to foreign proteins or drugs.

- Hives, itching, rash, difficulty breathing with cough or wheezing, swelling around the mouth and throat, tightness of the chest, dizziness or fainting, and low blood pressure are all symptoms of a severe allergic reaction (anaphylaxis). Call 911 should you experience one or more of these symptoms.

These are not all the possible side effects of SEVENFACT. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1- 800-FDA-1088.

HOW SHOULD I STORE SEVENFACT?

- SEVENFACT should be stored in its product packaging to protect from light.
- Prior to reconstitution, the SEVENFACT kit should be stored at room temperature but can be stored between 36°F to 86°F (2°C to 30°C).
- After reconstitution, SEVENFACT should be stored at room temperature but can be stored between 36°F to 86°F (2°C to 30°C), for up to 4 hours.
- SEVENFACT should not be frozen.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF SEVENFACT

This leaflet summarizes the most important information about SEVENFACT.

Do not use SEVENFACT for a condition for which it was not prescribed. Do not give SEVENFACT to other people even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about SEVENFACT that is written for health professionals.

For more information, go to www.SEVENFACT.com or call 855.718.HEMA (4362).

WHAT ARE THE INGREDIENTS IN SEVENFACT?

Active ingredient: coagulation factor VIIa (recombinant)-jncw

INACTIVE INGREDIENTS: ARGININE HYDROCHLORIDE, GLYCINE, ISOLEUCINE, LYSINE HYDROCHLORIDE, POLYSORBATE 80, TRISODIUM CITRATE DIHYDRATE, HYDROCHLORIC ACID, NITROGEN AND WATER FOR INJECTION.

FOR INFORMATION CONTACT:

HEMA Biologics, LLC
4441 Springdale Road
Louisville, Kentucky 40241-1086

Manufactured by:
Laboratoire Francais du Fractionnement et des Biotechnologies S.A. (LFB S.A.)
Les Ulis, 91940
France

Distributed by:
HEMA Biologics
Louisville, KY 40241

U.S. License No. 2061

PATENT Information: https://hemabiodup.wpengine.com/patents/

Approved 04/2020

HEMA Biologics

rare disorders first drafted in 2018, including Guidance for Industry: Human Gene Therapy for Hemophilia and Guidance for Industry: Human Gene Therapy for Rare Diseases. FDA also confirmed draft recommendations, Guidance for Industry: Long Term Follow- Up After Administration of Human Gene Therapy Products, to follow patients for safety for five to 15 years after participating in a CGT clinical trial.

The framework also updated guidance for best practices for manufacturers to make and test new CGT products, Guidance for Industry: Chemistry, Manufacturing, and Control Information for Human Gene Therapy, Investigational New Drug Applications. Finally, a new draft guidance was published to help clarify that products treating rare disease must be unique (i.e., not "sameness" such as minor variations of the same cell or genetic material) to apply for orphan drug status, which gives certain incentives like tax credits, FDA fee waivers and rights to market a new drug exclusively (or without competitors selling the same drug) for seven years after approval, Guidance for Industry: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations. This guidance framework clarified many of the issues facing developers of cell and gene treatments for hemophilia and other rare bleeding disorders.

THE NEW LANDSCAPE FOR HEMOPHILIA CGT

In 2021, more than a dozen gene transfer, gene editing and genetically modified cell therapy trials for hemophilia are ongoing, with AAV gene therapies the furthest along though lentivirus gene therapy and non-viral genetically modified cell therapies clinical trials. The outbreak of the respiratory disease COVID-19 caused by the novel coronavirus SARS-CoV-2, and passage of the Coronavirus Aid, Relief, & Economic Security Act of 2020 by Congress has shifted the focus of FDA. In January 2021, FDA added recommendations for CGT manufacturers to its guidance framework, Guidance for Industry: Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency.

CGT FOR HEMOPHILIA IN 2021 AND BEYOND

Despite many challenges for ongoing clinical trials in 2020, CGT treatments for hemophilia are much closer to reaching patients. Many clinical trials have benefited from wide adoption of digital health and telemedicine in 2020, and from the additional standardization of CGT manufacturing practices under the updated FDA guidance framework.

The CGT community has taken important early steps on the path to harmonization or development of international recommendations applicable across the world. However, several hemophilia gene therapy trials have also experienced setbacks related to making or distributing CGT products during the COVID-19 outbreak and delays to clinical trials while new scientific and safety information is being investigated and shared with FDA. Such communication between product developers and regulatory agencies, such as FDA, is a very important part of developing safe and effective treatments. The COVID-19 outbreak could also increase the time it takes for these treatments to become widely available. While current guidance framework has helped streamline development of CGT, we expect that FDA will continue to work closely with researchers, product developers and patient groups to further evolve the CGT guidance framework to help ensure that the next generation of hemophilia treatments are developed rapidly, efficiently and safely.

A Look at the **DRUG RECALL PROCESS**

BY HFA STAFF

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. 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. 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, 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, 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. 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 anything we can go to get.

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, 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 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 manufacturer. After a recall has begun, the recall is entered in the Recall Enterprise System. The RES is a database used by FDA to submit, update, classify and terminate recalls.

FDA Mandated Recalls

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. 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.

Recent Recalls of Products Indicated for Treatment of Bleeding Disorders

Product	Manufacturer	Date	Issue	Scope	Action taken
Mononine	CSL Behring	January 21, 2021	Manufacturing deviation that occurred during the filling process.	1 lot in United States; other lots worldwide	Voluntary pharmacy-level recall. Manufacturer stated "patients can continue to use product they may have. Although the potential for safety risk to patients is considered low, it cannot be fully excluded." Note: Product was discounted in Septemeber 2020; product was expected to be available through mid-2021.
Tranexamic acid injection	Mylan	September 1, 2020	Some carton/package labels may have been mislabeled as an unrelated product, Amiodarone HCl Injection.	4 lots	Voluntary recall to the hospital/clinic level. Product is exclusively used in inpatient setting.
Stimate nasal spray	Ferring Pharmaceuticals (Distributor: CSL Behring)	July 21, 2020	Product testing revealed low volume and therefore above-specification concentration of active ingredient	All product worldwide	Voluntary recall (initiated as pharmacy-level recall; subsequently extended to consumer-level). Manufacturer does not anticipate product becoming available before second half of 2023.
VONVENDI	Takeda	February 25, 2020	Internal manufacturer audit revealed "one step did not proceed as expected." Manufacturer informed FDA during its regular on-site inspection and received "feedback on how [they] could improve." Manufacturer subsequently recalled vials from lots manufactured during this period, despite finding no impact on product safety or efficacy.	2 lots, 3425 vials, U.S. only	Voluntary pharmacy level recall.
Humate-P	CSL Behring	October 15, 2019	Printing misalignment on label could lead to confusion on dosage/potency	Lots of all fill sizes (600, 1200, 2400 Ius)	No recall. Drug information alert issued by manufacturer.
Hemlibra	Genentech	October 5, 2019	Particulate matter outside specifications found in vials (product deviation, not contamination)	Found in 1 batch during routine inspection	No recall (regulators agreed there was no change in product benefit/risk profile). Genentech notified U.S., European, Canadian and Japanese health authorities in March 2019.
Hemlibra	Genentech (through contract specialty pharmacy Medvantx)	September 21, 2019	Injection needles of incorrect length included in shipment to patients who receive product through the Genentech Patient Foundation	124 families and 92 health care providers; shipments involved took place over ~2 months	No recall; Genentech notified FDA via standard U.S. drug safety reporting.
Kogenate FS	Bayer	July 19, 2019	Mislabeling resulted in distribution of wrong product, wrong dosage, post-expiration	2 lots, 900+ vials, distributed over period of 6 months	Class 2 voluntary recall to end user.

CURRENT PRODUCTS
AVAILABLE FOR TREATMENT OF BLEEDING DISORDERS

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.

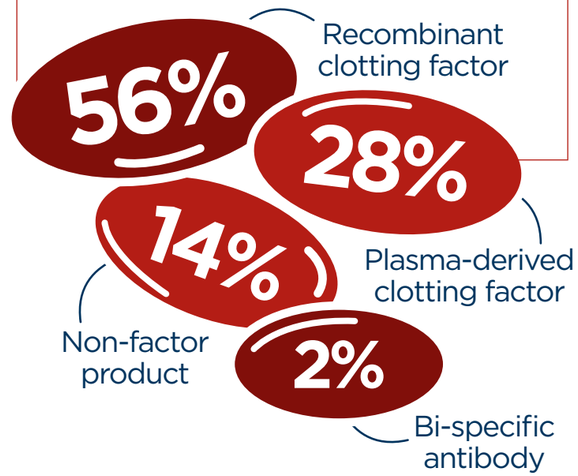
Information in this issue should not be interpreted as medical advice. We encourage frequent dialogue with experienced health care professionals regarding your health and the therapies used to treat your bleeding disorder.

43 APPROVED PRODUCTS BY THE NUMBERS:

DISTRIBUTION OF PRODUCTS BY MANUFACTURER

TAKEDA	8
CSL BEHRING	6
NOVO NORDISK	5
PFIZER, INC.	4
BAYER	3
GRIFOLS, INC	3
OCTAPHARMA USA, INC.	3
FERRING PHARMACEUTICALS	2
SANOFI GENZYME	2
AKORN PHARMACEUTICALS	1
BIO PRODUCTS LABORATORY USA, INC.	1
DR. REDDY'S LABORATORIES	1
GENENTECH	1
HEMA BIOLOGICS	1
KEDRION BIOPHARMA	1
MEDEXUS	1

PRODUCTS BY TYPE



NUMBER OF PRODUCTS BY INDICATION

MOST RECENTLY RELEASED PRODUCTS

YEAR RELEASED	PRODUCT	INDICATION	MANUFACTURER
2020	SEVENFACT	Inhibitor	HEMA Biologics
2020	Desmopressin Acetate Injection USP (desmopressin acetate)	Factor VIII; vWD	Dr. Reddy's Laboratories
2019	Novo Nordisk	Factor VIII	ESPEROCT
2018	Bayer	Factor VIII	Jivi

LIST OF APPROVED PRODUCTS

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

Advate
Takeda • Factor VIII

Adynovate
Takeda • Factor VIII

Afstyla
CSL Behring • Factor VIII

Alphanate
Grifols, Inc • Factor VIII;vWD

Aphanine SD
Grifols, Inc • Factor IX

Alprolix
Sanofi Genzyme • Factor IX

Amicar
(amniocaproic acid - oral solution and tablets)
Akorn Pharmaceuticals • Other

BeneFIX
Pfizer, Inc. • Factor IX

Coagadex
Bio Products Laboratory USA, Inc. • Rare

Corifact
CSL Behring • Rare

Cyklokapron
(tranexamic acid injection)
Pfizer, Inc. • Factor VIII; Factor IX

DDAVP (Desmopressin)
Ferring Pharmaceuticals • Factor VIII;vWD

Desmopressin Acetate Injection USP
(desmopressin acetate)
Dr. Reddy's Laboratories • Factor VIII;vWD

Eloctate
Sanofi Genzyme • Factor VIII

ESPEROCT
Novo Nordisk • Factor VIII

FEIBA NF
Takeda • Inhibitor

FIBRYGA
Octapharma USA, Inc. • Rare

HEMLIBRA
Genetech • Factor VIII;Inhibitor

Hemofil M
Takeda • Factor VIII

Humate-P
CSL Behring • Factor VIII;vWD

Idelvion
CSL Behring • Factor IX

IXINITY
Medexus • Factor IX

Jivi
Bayer • Factor VIII

Koate
Kedrion Biopharma • Factor VIII

Kogenate FS
Bayer • Factor VIII

Kovaltry
Bayer • Factor VIII

Lysteda
(tranexamic acid tablets)
Ferring Pharmaceuticals • Other

Novoeight
Novo Nordisk • Factor VIII

NovoSeven RT
Novo Nordisk • Factor VIII

NUWIQ
Octapharma USA, Inc. • Factor VIII

Obizur
Takeda • Rare

Profilnine
Grifols, Inc • Factor IX

REBINYN
Novo Nordisk • Factor IX

Recombinate
Takeda • Factor VIII

RiaSTAP
CSL Behring • Rare

Rixibis
Takeda • Factor IX

SEVENFACT
HEMA Biologics • Inhibitor

Stimate
(Desmopressin Nasal Spray)
CSL Behring • Factor VIII;vWD

Tretten
Novo Nordisk • Rare

Vonvendi
Takeda • vWD

Wilate
Octapharma USA, Inc • Factor VIII;vWD

Xyntha
Pfizer, Inc • Factor VIII

Xyntha/Xyntha Solofuse
Pfizer, Inc • Factor VIII

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.

Manufacturer
Company that produces and sells the therapy.

Product Type
Indicated method used to create product.

Specific Product Type
Detailed classification of product type, if applicable.

Half Life
Amount of time a product stays intact in the bloodstream until its efficacy is halved.

FDA Approved
Year the product was approved for treatment by FDA.

Indications
Bleeding disorder type/factor deficiency the therapy is intended to treat.

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 FDA. 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 2021. 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

FACTOR VIII

Product	Manufacturer	Product Type	Specific Product Type	Half-Life	FDA Approval Date	Indications	Notes
Advate	Takeda	Recombinant clotting factor	Antihemophilic factor (recombinant)	Adults(>16 years)= 12.0 ± 4.2 hrs ; 12 to <16 yrs= 12.0 ± 2.9; 5 to <12 yrs=11.2 ± 3.5 hrs; 2 to <5 yrs=9.5 ± 1.8 hrs; 1 month to <2 yrs=8.7 ± 1.4 hrs	2003	Factor VIII	
Adynovate	Takeda	Recombinant clotting factor	Antihemophilic factor (recombinant), PEGylated	18 years= 14.69 ± 3.79 hrs; 12 to <18 years= 13.43 ± 4.05 hrs; 6 to <12 years= 12.4 ± 1.67 hrs; <6 years= 11.8 ± 2.43 hrs. Overall 1.3-1.5 half-life extension compared to ADVATE	2015	Factor VIII	
Afstyla	CSL Behring	Recombinant clotting factor		After single dose of 50 IU/kg: Adults (≥18 years): 14.2 hours (mean); Adolescents (≥12 to <18 years): 14.3 hours (mean); Children: (0 to <6 yrs): 10.4 hours (mean); (≥6 to <12 years): 10.2 hours (mean)	2016	Factor VIII	
Alphanate	Grifols, Inc	Plasma-derived clotting factor		17.9	1978	Factor VIII; vWD	
Cyklokapron (tranexamic acid injection)	Pfizer, Inc.	Non-factor product	Antifibrinolytic agent	2 hours[f]	1986	Factor VIII; Factor IX	f-terminal elimination phase g-indicated 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. Prescribing Information at www.pfizermedicalinformation.com/en-us/patient
DDAVP (Desmopressin)	Ferring Pharmaceuticals	Non-factor product	Intravenous injection-factor catalyst /factor booster/factor precipitator		1978	Factor VIII; vWD	
Desmopressin Acetate Injection USP (desmopressin acetate)	Dr. Reddy's Laboratories	Non-factor product	Intravenous injection-factor catalyst /factor booster/factor precipitator		2020	Factor VIII; vWD	
Eloctate	Sanofi Genzyme	Recombinant clotting factor		19.7 hours (17.4, 22.0) in adults Pediatric: 12 to 17 years: 16.4 hours (14.1, 18.6) 6 to 11 years: 14.9 hours (12.0, 17.8) 1 to 5 years: 12.7 hours (11.2, 14.1)	2014	Factor VIII	PK parameters were determined after a single 50 IU/KG dose.
ESPEROCT	Novo Nordisk	Recombinant clotting factor		22 hours (mean) fixed dosing regimen of one injection every four days for adolescents or adults, or every three to four days in children.	2019	Factor VIII	
HEMLIBRA	Genentech	Bi-Specific Antibody	Therapeutic bi-specific antibody	26.9 +/- 9.1 days (mean +/- SD)	2017	Factor VIII; Inhibitor	2017 for inhibitors, 2018 for non-inhibitors. Additional route of delivery information: humanized, monoclonal, subcutaneous injection
Hemofil M	Takeda	Plasma-derived clotting factor	Antihemophilic factor (human) method m, monoclonal Purified	14.8 ± 3.0 hrs	1966	Factor VIII	

Product	Manufacturer	Product Type	Specific Product Type	Half-Life	FDA Approval Date	Indications	Notes
Humate-P	CSL Behring	Plasma-derived clotting factor		12.2 hours (mean) in Hemophilia A; 10-11 hours (median) for VWD	1986	Factor VIII; vWD	
Jivi	Bayer	Recombinant clotting factor	Antihemophilic factor [recombinant], PEGylated-aucl	17.9 hours	2018	Factor VIII	Extended half-life
Koate	Kedrion Biopharma	Plasma-derived clotting factor		16.1	1974	Factor VIII	
Kogenate FS	Bayer	Recombinant clotting factor	Antihemophilic factor [recombinant]	Adults: 13.74 hours Children: 10.7 hours	1993	Factor VIII	
Kovaltry	Bayer	Recombinant clotting factor	Antihemophilic factor [recombinant]	0 to <6 yrs : 12.1 hours 6 to <12 yrs: 12.0 hours 12 to 17 yrs: 14.4 hours ≥18 yrs: 14.2 hours	2016	Factor VIII	
Novoeight	Novo Nordisk	Recombinant clotting factor		Adults/adolescents—One Stage Clotting Assay: 10.8 hours; Chromogenic Assay: 12.0 hours. Pediatrics—One Stage Clotting Assay: 0-<6 yo - 7.7 hours, 6-<12 yo - 8.0 hours; Chromogenic Assay: 0-<6 yo - 10.0 hours, 6-<12 yo - 9.4 hours	2013	Factor VIII	
NUWIQ	Octapharma USA, Inc.	Recombinant clotting factor	Antihemophilic recombinant clotting factor	17.1 +/- 11.2hrs. (Adults); 13.1 +/- 2.6hrs. (6-≤12 yrs.); 11.9 +/- 5.4hrs. (2-5 yrs.)	2015	Factor VIII	NUWIQ is a recombinant FVIII produced in human cells without chemical modication or protein fusion.
Recombinate	Takeda	Recombinant clotting factor	Antihemophilic factor (recombinant)	14.6 ± 4.9 hrs	1992	Factor VIII	Half-life 11.2 ± 2.5 vs Advate
Stimate (Desmopressin Nasal Spray)	CSL Behring	Non-factor product	Nasal spray	3.3-3.5 hours	1994	Factor VIII; vWD	
Wilate	Octapharma USA, Inc.	Plasma-derived clotting factor		VWF: 15.8 hours; FVIII: 19.6 hours	2009	Factor VIII; vWD	Prophylaxis trial underway
Xyntha	Pfizer, Inc.	Recombinant clotting factor		11.2 ± 5.0 hours[a,b]	2008	Factor VIII	a-Results from 30 previously treated patients (PTPs) 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA. b-Compared to adults, the half-life of XYNTHA is shorter in children and the clearance (based on per kg body weight) is approximately 40% higher in children. Prescribing Information at www.pfizermedicalinformation.com/en-us/patient
Xyntha/Xyntha Solofuse	Pfizer, Inc.	Recombinant clotting factor		11.2 ± 5.0 hours[a,b]	2008	Factor VIII	a-Results from 30 previously treated patients (PTPs) 12 to 60 years old, who received a single infusion of 50 IU/kg XYNTHA. b-Compared to adults, the half-life of XYNTHA is shorter in children and the clearance (based on per kg body weight) is approximately 40% higher in children. Prescribing Information at www.pfizermedicalinformation.com/en-us/patient

FACTOR IX

Product	Manufacturer	Product Type	Specific Product Type	Half-Life	FDA Approval Date	Indications	Notes
Alphanine SD	Grifols, Inc	Plasma-derived clotting factor			1990	Factor IX	
Alprolix	Sanofi Genzyme	Recombinant clotting factor		50 IU/KG: ADULTS - 86.52 Hrs (37.2%). PEDIATRIC - 12 to 17 years: 80 hours (15%); 6 to 11 years: 72 hours (23%); 2 to 5 years: 68 hours (24%). 100 IU/KG: ADULTS - 97 Hrs (35%). PEDIATRIC - 12 to 17 years: 94 hours (24%)	2014	Factor IX	
BeneFIX	Pfizer, Inc.	Recombinant clotting factor		18.8 ± 5.4 hours (range 11 to 36 hours)[d,e]	1997	Factor IX	d-Results from 37 previously treated adult patients (>15 years old) after single intravenous dose of 50 IU/kg BeneFIX given as a 10-minute infusion. e-The mean ± standard deviation t½ in 13 children aged ≥2 years to <12 years and 6 adolescents aged ≥12 years to ≤15 years was 19.8 ± 4.0h and 21.1 ± 4.5h, respectively. www.pfizermedicalinformation.com/en-us/patient
Cyklokapron (tranexamic acid injection)	Pfizer, Inc.	Non-factor product	Antifibrinolytic agent	2 hours[f]	1986	Factor VIII; Factor IX	f-terminal elimination phase g-indicated 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. Prescribing Information at www.pfizermedicalinformation.com/en-us/patient
Idelvion	CSL Behring	Recombinant clotting factor		After single dose of 50 IU/kg: Adults: 104 hours; Adolescents (12 to <18 years): 87 hours (mean); Children: (0 to <6 years): 90 hours (mean); and (6 to <12 years): 93 hours (mean)	2016	Factor IX	
IXINITY	Medexus	Recombinant clotting factor		24 hours	2015	Factor IX	Pediatric trial underway
Profilnine	Grifols, Inc	Plasma-derived clotting factor			1990	Factor IX	
REBINYN	Novo Nordisk	Recombinant clotting factor		Single Dose: ≤ 6 years – 69.6 hours; 7-12 years old – 76.3 hours; 13-17 years old – 89.4 hours; ≥ 18 years old – 83.0 hours. Steady state: 13 – 17 years old 103.1 hours; ≥ 18 years old – 114.9 hours*	2017	Factor IX	Limitations of Use: REBINYN® is not indicated for routine prophylaxis in the treatment of patients with hemophilia B. REBINYN® is not indicated for immune tolerance induction in patients with hemophilia B
Rixibis	Takeda	Recombinant clotting factor	Coagulation factor IX (recombinant)	≥12 years= 25.7 ± 1.5 hrs; 6 -<12 years= 23.2 ± 1.6 hrs; <6 years= 27.7 ± 2.7 hrs	2013	Factor IX	

INHIBITOR

Product	Manufacturer	Product Type	Specific Product Type	Half-Life	FDA Approval Date	Indications	Notes
FEIBA NF	Takeda	Plasma-derived clotting factor	Anti-inhibitor coagulant complex	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	1986	Inhibitor	Prophylaxis indication 2013. Plasma-Derived Clotting Factor containing primarily non-activated FII, FIX and FX and activated FVII, and small amounts of FVIII antigen
HEMLIBRA	Genentech	Bi-specific antibody	Therapeutic bi-specific antibody	26.9 +/- 9.1 days (mean +/- SD)	2017	Factor VIII; Inhibitor	2017 for inhibitors, 2018 for non-inhibitors Additional route of delivery information: humanized, monoclonal, subcutaneous injection
NovoSeven RT	Novo Nordisk	Recombinant clotting factor		Hemophilia A or B — Adolescents/Adults (15-63 yrs): 2.9- 3.1 hours; Pediatrics (2-12 yrs): 2.6 hours FVII Deficiency — Adolescents/Adults (20-43 yrs): 2.8-3.1 hours	1999	Inhibitor; Rare	
SEVENFACT	HEMA Biologics	Recombinant clotting factor	Recombinant factor VIIa	Hemophilia A or B—Adolescents/Adults (15-63 yrs): 2.9- 3.1 hours; Pediatrics (2-12 yrs): 2.6 hours. FVII Deficiency—Adolescents/Adults (20-43 yrs): 2.8-3.1 hours	2020	Inhibitor	Received FDA approval in April 2020. Now avaliable as of January 2021.

vWD

Product	Manufacturer	Product Type	Specific Product Type	Half-Life	FDA Approval Date	Indications	Notes
Alphanate	Grifols, Inc	Plasma-derived clotting factor		17.9	1978	Factor VIII; vWD	
DDAVP (Desmopressin)	Ferring Pharmaceuticals	Non-factor product	Intravenous injection-factor catalyst/ factor booster/factor precipitator		1978	Factor VIII; vWD	
Desmopressin Acetate Injection USP (desmopressin acetate)	Dr. Reddy's Laboratories	Non-factor product	Intravenous injection-factor catalyst/ factor booster/factor precipitator		2020	Factor VIII; vWD	
Humate-P	CSL Behring	Plasma-derived clotting factor		12.2 hours (mean) in Hemophilia A; 10-11 hours (median) for VWD	1986	Factor VIII; vWD	
Stimate (Desmopressin Nasal Spray)	CSL Behring	Non-factor product	Nasal spray	3.3-3.5 hours	1994	Factor VIII; vWD	
Vonvendi	Takeda	Recombinant clotting factor	von Willebrand factor (recombinant)	For 50IU/kg mean hours (SD) 22.6 (5.34)	2015	vWD	
Wilate	Octapharma USA, Inc.	Plasma-derived clotting factor		VWF: 15.8 hours; FVIII: 19.6 hours	2009	Factor VIII; vWD	Prophylaxis trial underway

RARE

Product	Manufacturer	Product Type	Specific Product Type	Half-Life	FDA Approval Date	Indications	Notes
Coagadex	Bio Products Laboratory USA, Inc.	Plasma-derived clotting factor	Lyophilized powder for solution for intravenous injection	Patients 12 years and older: 30.3 hours Children < 12 years	2015	Rare	* The half-life in children < 12 years has not been evaluated. However, incremental recovery (IR) in children <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 <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.
Corifact	CSL Behring	Plasma-derived clotting factor		6.6 hours by Berichrom Assay method (mean)	2011	Rare	
FIBRYGA	Octapharma USA, Inc.	Plasma-derived clotting factor		75.9 hours (mean)	2017	Rare	
NovoSeven RT	Novo Nordisk	Recombinant clotting factor		Hemophilia A or B—Adolescents/Adults (15-63 yrs): 2.9- 3.1 hours; Pediatrics (2-12 yrs): 2.6 hours. FVII Deficiency—Adolescents/Adults (20-43 yrs): 2.8-3.1 hours	1999	Inhibitor; Rare	
Obizur	Takeda	Recombinant clotting factor	Antihemophilic factor (recombinant), porcine sequence	Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses	2014	Rare	
RiaSTAP	CSL Behring	Plasma-derived clotting factor		78.7 hours (mean)	2009	Rare	
Tretten	Novo Nordisk	Recombinant clotting factor		Adults: 5.1 hrs Pediatrics: 7.1 hrs	2013	Rare	

OTHER

Product	Manufacturer	Product Type	Specific Product Type	Half-Life	FDA Approval Date	Indications	Notes
Amicar (amniocaproic acid - oral solution and tablets)	Akorn Pharmaceuticals	Non-factor product	Oral Solution and Tablets	n/a	1998	Other	
Lysteda (tranexamic acid tablets)	Ferring Pharmaceuticals	Non-factor product	Tablet	n/a	1986	Other	Tablet/650mg

We're counting down the days
for HFA hugs to resume

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you and your family
at **www.hemophiliafed.org**

A TUMULTUOUS YEAR,
Few Changes for Treatment Options

BY HFA STAFF

Our last product guide hit the presses in early April 2020, right as the coronavirus caused the world to come to a screeching halt. At the time, many assumed a few weeks of lockdowns would control the virus. Yet here we are a year later, with almost everything we considered to be a temporary change now seemingly a normal part of life. More than 30.5 million cases were confirmed in the U.S., taking the lives of more than 550,000 people. Amidst the tragedy and suffering, the scientific and medical communities responded in heroic ways. From frontline workers to the teams implementing a testing network that conducted more than 376 million tests, the response to the pandemic demonstrated the potential that exists when we work together.

In just 10 months, the pharmaceutical industry, using years of work and research findings, was able to create, research, manufacture and begin distributing vaccines that have been proven safe and effective at preventing death from COVID-19. Since January, more than 200.5 million doses of vaccine have been delivered to states, with about 2.9 million doses administered per day on average.

Routine medical procedures and treatments were upended during the pandemic, and people living with a bleeding disorder saw changes to systems that were permanent fixtures in their lives. With many hospitals and Hemophilia Treatment Centers closed for anything but COVID-19 treatment, community members were forced to change their routines. One mom of a 3-year-old boy with hemophilia shared that she began to use her local pediatrician's office to assist with infusions on a weekly basis, instead of driving into the city to visit the HTC, which was in a large hospital. A mom of a teenage son with hemophilia shared a positive experience with their Annual Comp Clinic, now taking place as a telehealth visit. This process, which previously lasted hours in person, has been shortened substantially. Through telehealth, medical providers still provided high-quality individual care, even going so far as to measure joint range of motion over the video screen.

While the world was changing fast in almost every other sense, the list of treatment options available for bleeding disorders experienced a quiet year with no major changes. Though, this year's list does reflect some edits:

- **Desmopressin Acetate Injection—new product addition—**Launched for FVIII in May 2020 by Dr. Reddy's Laboratories, this drug is a generic version of DDAVP. DDAVP is the licensed/trademark name owned by Ferring Pharmaceuticals.
- **Wilate—new indication listed for Factor VIII—**This product, manufactured by Octapharama, has been available for treatment of vWD since 2009 but was approved for treatment of Factor VIII in October 2019. This was not reflected on our product charts last year by omission.
- **Mononine—removed from available products—**CSL Behring announced in 2020 that it would no longer be distributing or manufacturing this factor IX treatment, saying, "Over time, patients have transitioned from older therapies to newer, next generation treatment options, and very few patients currently remain on MONONINE in the U.S."

The future of treatment for bleeding disorders continues to be an exciting topic for our community. In our emerging therapies charts, you'll find 53 clinical trials currently underway, investigating the efficacy and safety of 30 investigational therapeutic products. While these things don't happen overnight, years of research have led to this moment in which our community could see several product approvals in the next few years, some that could drastically affect the way people with a bleeding disorder receive care.

US Food and Drug Administration's Drug Approval Processs

What is a drug, as defined by 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:

Drug Developed

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

1

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.

2

IND Application

The sponsor submits an Investigational New Drug application to 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.

IND Review:

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.

CLINICAL

Drug Sponsor's Clinical Studies/Trials

20-80 healthy volunteers

3

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.

100s of patients

4

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, FDA and sponsors discuss how large-scale studies in Phase 3 will be conducted.

1000s of patients

5

Phase 3

1000s: 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.

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.

NDA REVIEW

FDA's New Drug Application Review

6

Review Meeting

FDA meets with a drug sponsor prior to submission of a new drug application.

7

NDA Application

The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an 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.

8-9

Application Reviewed

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

10

Drug Labeling

FDA reviews the drug's professional labeling and ensures appropriate information is communicated to health care professionals and consumers.

11

Facility Inspection

FDA inspects the facilities where the drug will be manufactured.

12

Drug Approval

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.

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 FDA's post-marketing safety system is meant to detect serious unexpected adverse events and take definitive action when needed.

Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA.

FDA's MedWatch voluntary system makes it easier for physicians and consumers to report adverse events. Usually, when important new risks are uncovered, the risks are added to the drug's labeling and the public is informed of the new information through letters, public health advisories and other educational means. In some cases, the use of the drug might be substantially limited. And in rare cases, the drug might need to be withdrawn from the market.

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.

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 10 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 FDA must be reviewed, approved and monitored by an institutional review board. 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

EARLY PHASE 1:
(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 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.

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?

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EMERGING THERAPIES

UNDERGOING CLINICAL TRIALS 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 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

AAV5-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 elaparvovec
Factor IX

Fitusiran/SAR439774
Factor VIII; Factor IX; Inhibitor

FLT180a
Factor IX

giroctocogene fitelparvovec
Factor VIII

giroctocogene fitelparvovec, fidanacogene elaparvovec
Factor VIII; Factor IX

marstacimab
Factor VIII; Factor IX; Inhibitor

Marzeptacog alfa (activated)
Factor IX

MOD-5014
Factor IX; Rare

NNC0365-3769 A (Mim8)
Factor VIII; Inhibitor

SB-525
Factor VIII

SB-FIX
Factor VIII

scAAV2/8-LP1-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

30 INVESTIGATIONAL THERAPEUTIC PRODUCTS IN 53 CLINICAL TRIALS *BY THE NUMBERS:*

TYPE OF INVESTIGATIONAL THERAPEUTIC PRODUCT UNDERGOING TRIAL

24 | GENE THERAPY

11 | NOVEL: INVESTIGATIONAL FACTOR PRODUCT

10 | NOVEL: NON-FACTOR PRODUCT

8 | RECOMBINANT CLOTTING FACTOR

COMPANIES RUNNING THE MOST TRIALS

SANOFI GENZYME	12
PFIZER, INC.	6
BIOMARIN PHARMACEUTICAL	5
HEMA BIOLOGICS	3
NOVO NORDISK	3
TAKEDA	3
UNIQURE	3

CLINICAL TRIALS BY INDICATION*

FACTOR VIII | FACTOR IX | INHIBITOR | RARE

*Note, one clinical trial can research more than one indication

STAGES OF ONGOING CLINICAL TRIALS

Read about the drug approval process and states of clinical trials on page 38.

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 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:

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.

Sponsor
Company that is researching/studying a product/trial.

Type
Method used to create the product/therapy.

Specific Product Type
Detailed classification of type, if applicable.

Phase
The current stage in the FDA approval process.

Indications
Bleeding disorder type/factor deficiency the therapy is intended to treat.

Indication Details
Detailed classification of indication, if applicable.

Official Title of Study
Submitted to 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 FDA. 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 2021. 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

FACTOR VIII

Investigational Therapeutic Product Name	Sponsor	Type	Specific Type	Phase	Indications	Indication Details	Official Title of Study	Notes
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor, who were previously under factor or BPA prophylaxtic treatment	A Study of Fitusiran in Severe Hemophilia A and B Patients Previously Receiving Factor or Bypassing Agent Prophylaxis (ATLAS-PPX)	
TAK-754	Takeda	Gene Therapy	Gene Transfer	Phase 1/2 - Active, not recruiting	Factor VIII	Hemophilia A	Safety and Dose Escalation Study of an Adeno-Associated Viral Vector for Gene Transfer in Hemophilia A Participants	
marstacimab	Pfizer, Inc.	Novel: Non-factor product	Antibody to Tissue Factor Pathway Inhibitor	Phase 3 - FDA Orphan Drug Status (HA), 2016 www.clinicaltrials.gov; NCT03938792	Factor VIII; Factor IX; Inhibitor	Severe hemophilia A or B (Factor VIII or Factor IX activity < 1%) Subjects enrolled as Factor VIII or Factor IX inhibitor patients must have a positive inhibitor test result (above the upper limit of normal) at the local laboratory and must receive a bypass agent as primary treatment for bleeding episodes	An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor <1%) Hemophilia A or B Patients with or without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis	
giroctocogene fitelparvovec	Pfizer, Inc.	Gene Therapy	Gene Transfer	Phase 3- FDA Orphan Drug Status, Fast Track status, Regenerative Medicine Advanced Therapy Designation; NCT04370054	Factor VIII	Moderately severe to severe hemophilia A adult subjects (FVIII:C <1%) who have completed at least 6 months of routine prophylaxis with FVIII products in the lead-in study C0371004	Study to Evaluate the Efficacy and Safety of PF-07055480 in Moderately Severe to Severe Hemophilia A Adults (AFFINE)	
SIG-001	Sigilon Therapeutics, Inc	Cell Therapy	Non-viral based encapsulated cell therapy	Phase 1,2 - FDA Orphan Drug Status (HA), 2019. Recruiting (NCT04541628)	Factor VIII	FVIII	A Phase 1, 2 Open-Label, Dose-Escalation, Safety, Tolerability, and Efficacy Study of SIG-001 in Adult Patients with Severe or Moderately-Severe Haemophilia A without Inhibitors	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.
giroctocogene fitelparvovec	Pfizer, Inc.	Gene Therapy	Gene Transfer	Phase 1/2 - FDA Orphan Drug Status, Fast Track status, FDA Regenerative Medicine Advanced Therapy Designation: July, 2019 NCT03061201; Trial was fully transitioned from Sangamo to Pfizer as of December 2019	Factor VIII	Severe hemophilia A (FVIII:C <1%) with >150 documented exposure days and no history of inhibitors who are negative for neutralizing antibodies	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	
SB-FIX	Sangamo Therapeutics	Gene Therapy	Genome Editing	Phase 1 - IND cleared. Orphan drug designation by FDA	Factor VIII	Severe IX	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	Active, not recruiting

Investigational Therapeutic Product Name	Sponsor	Type	Specific Type	Phase	Indications	Indication Details	Official Title of Study	Notes
SB-525	Sangamo Therapeutics	Gene Therapy		Phase 1/2 - IND cleared. Orphan drug designation by FDA and EMA. Fast track from FDA	Factor VIII	Severe VIII	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	Active, not recruiting. Sangamo Therapeutics, in partnership with Pfizer
concizumab	Novo Nordisk	Novel: Investigational factor product	Anti-TFPI	II - NCT03196284	Factor VIII; Factor IX	Congenital VIII and IX with inhibitors	A Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Haemophilia A and B Patients With Inhibitors (explorer™4)	
concizumab	Novo Nordisk	Novel: Investigational factor product	Anti-TFPI	II - NCT03196297	Factor VIII; Factor IX	Congenital VIII and IX	A Trial Evaluating Efficacy and Safety of Prophylactic Administration of Concizumab in Patients With Severe Haemophilia A Without Inhibitors (explorer™5)	
giroctocogene fitelparvovec, fidanacogene elaparvovec	Pfizer, Inc.	Gene Therapy	Gene Transfer	Phase 3 - NCT03587116	Factor VIII; Factor IX	Severe hemophilia A adult subjects (FVIII:C <1%) who are negative for nAb to AAV vector SB-525 capsid (AAV6) and moderately severe to severe hemophilia B (FIX:C <2%) who are negative for nAb to AAV vector Spark-100, prior to the respective therapeutic phase 3 gene therapy studies	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<2%) or Current FVIII Prophylaxis Replacement Therapy in Adult Hemophilia A Subjects (FIX:C<1%)	6-month lead-in study (phase 3)
NNC0365-3769 A (Mim8)	Novo Nordisk	Novel: Non-factor product	Coagulation factor VIII mimetic antibody	II - NCT04204408	Factor VIII; Inhibitor	Hemophilia A with or without Inhibitors	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	clinicaltrials.gov/ct2/show/NCT04204408?tem=mim8&draw=2&rank=1
SPK-8011	Spark Therapeutics, Inc.	Gene Therapy	Gene Transfer	Phase 1, Phase 2 - Orphan disease designation (January 2018); Breakthrough therapy designation (February 2018).	Factor VIII	VIII	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	
valoctocogene roxaparvovec	BioMarin Pharmaceutical Inc.	Gene Therapy	AAV Vector-Mediated Gene Transfer Therapy	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.	Factor VIII	Severe Hemophilia A	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	Active, not enrolling
BAY2599023 (DTX201)	Bayer	Gene Therapy		Phase 1/2 - Recruiting	Factor VIII	Severe Hemophilia A	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	Bayer in collaboration with Ultragenix Pharmaceuticals
SubQ-8	Octapharma USA, Inc.	Novel: Investigational factor product	Human-cl rhFVIII and Recombinant human von Willebrand Factor fragment dimer	Phase 1, Phase 2 - VIII	Factor VIII	VIII	Safety and Pharmacokinetics of Subcutaneous Injection of OCTA101 in Adult Patients With Severe Hemophilia A	

Investigational Therapeutic Product Name	Sponsor	Type	Specific Type	Phase	Indications	Indication Details	Official Title of Study	Notes
AAV2/8-HLP-FVIII-V3	St. Jude Children's Research Hospital	Gene Therapy	Gene Transfer	Phase 1	Factor VIII	VIII	GO-8: Gene Therapy for Haemophilia A Using a Novel Serotype 8 Capsid Pseudotyped Adeno-associated Viral Vector Encoding Factor VIII-V3	
Efanesoctocog Alfa (BIVV001)	Sanofi Genzyme	Novel: Investigational factor product	rFVIIIFc-XTEN	Phase 1 Phase 2	Factor VIII	VIII	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	
Efanesoctocog Alfa (BIVV001)	Sanofi Genzyme	Novel: Investigational factor product	rFVIIIFc-XTEN	Phase 1 Phase 2	Factor VIII	VIII	A Phase 1, Open-Label, Single-Site, Safety, Tolerability, and Pharmacokinetics Study of Repeat Doses of BIVV001	
Efanesoctocog Alfa (BIVV001)	Sanofi Genzyme	Novel: Investigational factor product	rFVIIIFc-XTEN	Phase 3	Factor VIII	VIII	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	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX	Hemophilia A and hemophilia B without inhibitor, who were previously under factor on demand treatment	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	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 1	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor	A Phase 1 Single-ascending and Multiple-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)	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 1 Phase 2	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor, who completed Phase 1 study	An Open-label Extension Study of an Investigational Drug, Fitusiran, in Patients With Moderate or Severe Hemophilia A or B	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with inhibitor, who were previously under BPA on demand treatment	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	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 2/3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with inhibitor, pediatric patients 1-11 years of age	Fitusiran Prophylaxis in Male Pediatric Subjects Aged 1 to Less Than 12 Years With Hemophilia A or B (ATLAS-PEDS)	
SPK-8016	Spark Therapeutics, Inc.	Gene Therapy	Gene Transfer	Phase 1, Phase 2	Factor VIII	VIII	Dose-finding Study of SPK-8016 Gene Therapy in Patients With Hemophilia A to Support Evaluation in Individuals With FVIII Inhibitors	
SCT800	Sinocelltech Ltd.	Recombinant clotting factor	Recombinant VIII	Phase 4	Factor VIII	Moderate to Severe VIII	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 Hemophilia A.	

Investigational Therapeutic Product Name	Sponsor	Type	Specific Type	Phase	Indications	Indication Details	Official Title of Study	Notes
SCT800	Sinocelltech Ltd.	Recombinant clotting factor	Recombinant VIII	Phase 3	Factor VIII	Severe VIII	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.	
valoctocogene roxaparvovec	BioMarin Pharmaceutical Inc.	Gene Therapy	AAV Vector-Mediated Gene Transfer Therapy	Phase 1/2	Factor VIII	Severe Hemophilia A	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	Recruiting by invitation
valoctocogene roxaparvovec	BioMarin Pharmaceutical Inc.	Gene Therapy	AAV Vector-Mediated Gene Transfer Therapy	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 2 019.	Factor VIII	Severe Hemophilia A	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	Active and Enrolling
valoctocogene roxaparvovec	BioMarin Pharmaceutical Inc.	Gene Therapy		Observational	Factor VIII	Hemophilia A	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	Active and Enrolling
valoctocogene roxaparvovec	BioMarin Pharmaceutical Inc.	Gene Therapy	AAV Vector-Mediated Gene Transfer Therapy	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 019.	Factor VIII	Severe Hemophilia A	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	Active, not enrolling
Efanesoctocog Alfa (BIVV001)	Sanofi Genzyme	Novel: Investigational factor product	rFVIIIFc-XTEN	Phase 3	Factor VIII	VIII	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	
Efanesoctocog Alfa (BIVV001)	Sanofi Genzyme	Novel: Investigational factor product	rFVIIIFc-XTEN	Phase 3	Factor VIII	VIII	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 <12	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor, who completed Phase 3 studies	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)	

FACTOR IX

Investigational Therapeutic Product Name	Sponsor	Type	Specific Product Type	Phase	Indications	Indication Details	Official Title of Study	Notes
AAV5-hFIXco-Padua/ AMT- 061	uniQure	Gene Therapy	Gene Transfer	Phase 2B - Breakthrough Designation; 1/30/17	Factor IX	IX	Phase IIb, 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 (AAV5-hFIXco-Padua, AMT-061)	
AAV5-hFIXco-Padua/ AMT- 061	uniQure	Gene Therapy	Gene Transfer	Phase 3 - Breakthrough Designation; 1/30/17	Factor IX	IX	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 (AAV5-hFIXco-Padua, AMT-061) Administered to Adult Subjec	Licensed to CSL Behring for Commercialization (pending government approval), Trial on Clinical Hold FDA, Dec. 2020
AMT-060 (AAV5-hFIX)	uniQure	Gene Therapy	Gene Transfer	Phase 1, Phase 2 - Breakthrough Designation; 1/30/17	Factor IX	IX	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 (AAV5-hFIX) Administered to Adult Patients With Severe or Moderately S	
APVO101 (IXINITY)	Medexus	Recombinant clotting factor	Recombinant Clotting Factor	Phase 3/4	Factor IX	FIX, pediatric (under 12 years of age)	Evaluation of a Recombinant Factor IX Product, APVO101, in Previously-Treated Pediatric Patients With Hemophilia B	
concizumab	Novo Nordisk	Novel: Investigational factor product	Anti-TFPI	II - NCT03196284	Factor VIII; Factor IX	Congenital VIII and IX with inhibitors	A Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Haemophilia A and B Patients With Inhibitors (explorer™4)	
concizumab	Novo Nordisk	Novel: Investigational factor product	Anti-TFPI	II - NCT03196297	Factor VIII; Factor IX	Congenital VIII and IX	A Trial Evaluating Efficacy and Safety of Prophylactic Administration of Concizumab in Patients With Severe Haemophilia A Without Inhibitors (explorer™5)	
fidanacogene elaparvovec	Pfizer, Inc.	Gene Therapy	Gene Transfer	Phase 2 - FDA Breakthrough Designation: July, 2016 FDA Orphan Drug Designation: September, 2015 www.clinicaltrials.gov; NCT03307980	Factor IX	Moderately severe to severe hemophilia B (FIX:C<2%) with >50 exposure days and no history of inhibitors who have previously received PF-06838435 and completed the C0371005 study	Long-term Safety and Efficacy Study and Dose-Escalation Substudy of PF 06838435 in Individuals With Hemophilia B	

Investigational Therapeutic Product Name	Sponsor	Type	Specific Product Type	Phase	Indications	Indication Details	Official Title of Study	Notes
fidanacogene elaparvovec	Pfizer, Inc.	Gene Therapy	Gene Transfer	Phase 3 - FDA Breakthrough Designation: July, 2016 FDA Orphan Drug Designation: September, 2015 www.clinicaltrials.gov; NCT03861273	Factor IX	Moderately severe to severe hemophilia B (FIX:C<2%) and no history of inhibitors who completed 6 months of routine Factor IX prophylaxis therapy during the lead in study (C0371004) and have >50 documented exposure days to a FIX protein product such as recombinant, plasma-derived or extended half-life FIX product	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)	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor, who were previously under factor or BPA prophylaxtic treatment	A Study of Fitusiran in Severe Hemophilia A and B Patients Previously Receiving Factor or Bypassing Agent Prophylaxis (ATLAS-PPX)	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX	Hemophilia A and hemophilia B without inhibitor, who were previously under factor on demand treatment	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	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 1	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor	A Phase 1 Single-ascending and Multiple-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)	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 1 Phase 2	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor, who completed Phase 1 study	An Open-label Extension Study of an Investigational Drug, Fitusiran, in Patients With Moderate or Severe Hemophilia A or B	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with inhibitor, who were previously under BPA on demand treatment	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	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 2/3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with inhibitor, pediatric patients 1-11 years of age	Fitusiran Prophylaxis in Male Pediatric Subjects Aged 1 to Less Than 12 Years With Hemophilia A or B (ATLAS-PEDS)	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hem A and Hem B with or without inhibitor, who completed Phase 3 studies	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)	
FLT180a	Freeline Therapeutics	Gene Therapy		Phase 2/3 - Long term follow up study	Factor IX	IX	A Study of Haemophilia B Patients Who Have Undergone Gene Therapy	Clincaltrials.gov link: https://clinicaltrials.gov/ct2/show/NCT03641703?term=FLT180a&rank=1

Investigational Therapeutic Product Name	Sponsor	Type	Specific Product Type	Phase	Indications	Indication Details	Official Title of Study	Notes
FLT180a	Freeline Therapeutics	Gene Therapy		Phase 1/2 - Open IND. Interventional study.	Factor IX	IX	A Factor IX Gene Therapy Study (FIX-GT) (FIX-GT)	Clinicaltrials.gov link: https://clinicaltrials.gov/ct2/show/NCT03369444?term=FL-T180a&rank=2
giroctocogene fitelparvovec, fidanacogene elaparvovec	Pfizer, Inc.	Gene Therapy	Gene Transfer	Phase 3 - NCT03587116	Factor VIII; Factor IX	Severe hemophilia A adult subjects (FVIII:C <1%) who are negative for nAb to AAV vector SB-525 capsid (AAV6) and moderately severe to severe hemophilia B (FIX:C <2%) who are negative for nAb to AAV vector Spark-100, prior to the respective therapeutic phase 3 gene therapy studies	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<2%) or Current FVIII Prophylaxis Replacement Therapy in Adult Hemophilia A Subjects (FIX:C<1%)	6-month lead-in study (phase 3)
marstacimab	Pfizer, Inc.	Novel: Non-factor product	Antibody to Tissue Factor Pathway Inhibitor	Phase 3 - FDA Orphan Drug Status (HA), 2016 www.clinicaltrials.gov; NCT03938792	Factor VIII; Factor IX; Inhibitor	Severe hemophilia A or B (Factor VIII or Factor IX activity < 1%) Subjects enrolled as Factor VIII or Factor IX inhibitor patients must have a positive inhibitor test result (above the upper limit of normal) at the local laboratory and must receive a bypass agent as primary treatment for bleeding episodes	An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor <1%) Hemophilia A or B Patients with or without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis	
Marzeptacog alfa (activated)	Catalyst Biosciences	Recombinant clotting factor	Recombinant FVIIa variant	Phase 2/3	Factor IX	VIII or IV with inhibitors	Open Label Phase 2/3 Study of Coagulation Factor VIIa Variant Marzeptacog Alfa (Activated) in Adult Subjects With Hemophilia A or B with inhibitors	
MOD-5014	OPKO Biologics	Novel: Investigational factor product	Long-acting Recombinant VIIa	Phase 1	Factor IX	VIII, IX with inhibitors	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	
scAAV2/8-LP1-hFIXco	St. Jude Children's Research Hospital	Gene Therapy	Gene Transfer	Phase 1	Factor IX	IX	An Open Label Dose-Escalation Study Of A Self Complementary Adeno-Associated Viral Vector (scAAV 2/8-LP1-hFIXco) For Gene Transfer in Hemophilia B	
TAK-748	Takeda	Gene Therapy	Gene Transfer	Phase 1/2 - Suspended (Reevaluation of development strategy)	Factor IX	Hemophilia B	A Phase 1/2 Study of SHP648, an Adeno-Associated Viral Vector for Gene Transfer in Hemophilia B Subjects	

INHIBITOR

Investigational Therapeutic Product Name	Sponsor	Type	Specific Product Type	Phase	Indications	Indication Details	Official Study Title	Notes
Coagulation FVIIa (Recombinant) Eptacog Beta or LR769	HEMA Biologics	Recombinant clotting factor	Coagulation VIIa, Recombinant, non-biosimilar	Phase 3b - Finalizing CSR	Inhibitor	Tratment of bleeding, Congenital VIII or IX with inhibitors: birth to <12 years	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 <12 years old with Inhibitors to Factor VIII or IX	
Coagulation FVIIa (Recombinant) Eptacog Beta or LR769	HEMA Biologics	Recombinant clotting factor	Coagulation VIIa, Recombinant, non-biosimilar	Phase 3 - Finalizing CSR	Inhibitor	Prevention of excessive bleeding, Congenital VIII or IX with inhibitors: elective surgery or other invasive procedures	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	
Coagulation FVIIa (Recombinant) Epta-cog Beta or LR769	HEMA Biologics	Recombinant clotting factor	Coagulation VIIa, Recombinant, non-biosimilar	Phase 1b - Open access published link: https://onlinelibrary.wiley.com /doi/epdf/10.1111/hae.13357	Inhibitor	Dose Ranging Study for VIII or IX with inhitors: ≥ 12 years	Dose-Ranging Study (N=15) Phase 1b Study Design Dose escalation, pharmacokinetics, safety and in vivo pharmacodynamics Ducore, et al. 2017 NCT01708564	
Dalcinonacog alfa (CB 2679d/ ISU304)	Catalyst Biosci-ences	Recombinant clotting factor	Recombinant IX	Phase 1/2	Inhibitor	IX	A Phase 1, Open-label, Multi-center, Dose-escalation Study to Investigate the Safety, Pharmacokinetics and Pharmacodynamics of ISU304 in Previously Treated Hemophilia B Patients	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia Bwith or without inhibitor, who were previously under factor or BPA prophylaxtic treatment	A Study of Fitusiran in Severe Hemophilia A and B Patients Previously Receiving Factor or Bypassing Agent Prophylaxis (ATLAS-PPX)	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 1	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor	A Phase 1 Single-ascending and Multiple-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)	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 1 Phase 2	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor, who completed Phase 1 study	An Open-label Extension Study of an Investigational Drug, Fitusiran, in Patients With Moderate or Severe Hemophilia A or B	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with inhibitor, who were previously under BPA on demand treatment	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	

Investigational Therapeutic Product Name	Sponsor	Type	Specific Product Type	Phase	Indications	Indication Details	Official Study Title	Notes
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 2/3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with inhibitor, pediatric patients 1-11 years of age	Fitusiran Prophylaxis in Male Pediatric Subjects Aged 1 to Less Than 12 Years With Hemophilia A or B (ATLAS-PEDS)	
Fitusiran/SAR439774	Sanofi Genzyme	Novel: Non-factor product	RNAi	Phase 3	Factor VIII; Factor IX; Inhibitor	Hemophilia A and hemophilia B with or without inhibitor, who completed Phase 3 studies	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)	
marstacimab	Pfizer, Inc.	Novel: Non-factor product	Antibody to Tissue Factor Pathway Inhibitor	Phase 3 - FDA Orphan Drug Status (HA), 2016 www.clinicaltrials.gov; NCT03938792	Factor VIII; Factor IX; Inhibitor	Severe hemophilia A or B (Factor VIII or Factor IX activity < 1%) Subjects enrolled as Factor VIII or Factor IX inhibitor patients must have a positive inhibitor test result (above the upper limit of normal) at the local laboratory and must receive a bypass agent as primary treatment for bleeding episodes	An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor <1%) Hemophilia A or B Patients with or without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis	
NNC0365-3769 A (Mim8)	Novo Nordisk	Novel: Non-factor product	Coagulation factor VIII mimetic antibody	II - NCT04204408	Factor VIII; Inhibitor	Hemophilia A With or Without Inhibitors	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	https://clinicaltrials.gov/ct2/show/NCT04204408?term=mim8&draw=2&rank=1

RARE

Investigational Therapeutic Product Name	Sponsor	Type	Specific Type	Phase	Indications	Indication Details	Official Title of Study	Notes
MOD-5014	OPKO Biologics	Novel: Investigational factor product	Long-acting Recombinant VIIa	Phase 1, Phase 2	Rare	Moderate to Severe VIII or IX with or without inhibitors	A Phase 1/2a, Open-Label, Multi-center, Dose Escalation Study to Assess the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) Profile of a Long Acting Recombinant FVIIa (MOD-5014) in Adult Men With Hemophilia A or B	
TAK-755	Takeda	Novel: Investigational factor product	Recombinant ADAMTS13	Phase 3 - Recruiting	Rare	Congenital/hereditary TTP	A Study of Prophylactic and On-demand Treatment of Congenital Thrombotic Thrombocytopenic Purpura (cTTP) With BAX 930 (rADAMTS13)	

vWD

No clinical trails of investigational therapeutic products for treatment of vWD were reported.

No clinical trails of investigational therapeutic products for treatment of other bleeding disorders were reported.

OTHER

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