ALL ABOUT **NOVEL THERAPIES**

OCTOBER 2025

PRODUCED BY Canadian Hemophilia Society
Help Stop the Bleeding

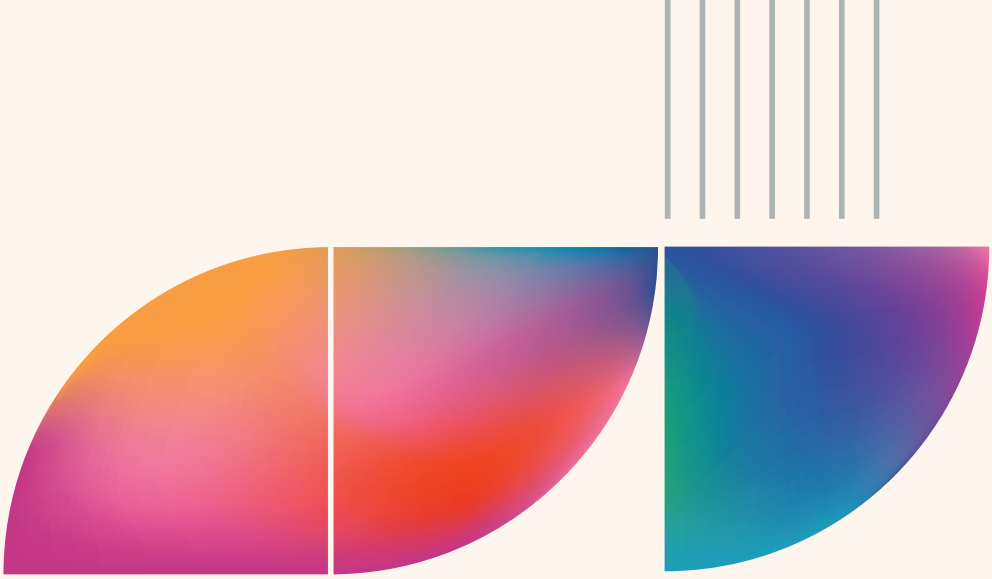

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TABLE OF CONTENTS

INTRODUCTION

Innovation is accelerating. Not just in communications, computer technology and artificial intelligence but also in medical science, including therapies for people with inherited bleeding disorders.

The last decade has seen significant treatment advances with the introduction of extended half-life factor VIII and IX concentrates and factor VIII mimetics like emicizumab. The first gene therapies have been introduced for both hemophilia A and B. The first rebalancing agents have been approved by health authorities. But those are just the start. Several different approaches to preventing and managing bleeding are in different stages of development, not only for hemophilia but also for von Willebrand disease and rare bleeding disorders that historically have received less research attention. This trend is sure to continue.

No longer do people with bleeding disorders have limited options among nearly identical products. They now have real choices among therapies which are very different in how they work and how they are administered. Moreover, options will likely increase in number in coming years. Decision-making will become more complex.

This online booklet, *All About Novel Therapies*, is a guide to these emerging therapies. Its goal is to provide people with bleeding disorders and their caregivers a basic understanding of novel therapies. This will help in shared decision-making with their health care providers when discussing and making treatment choices.

As treatment options are changing at a rapid pace, this booklet will be regularly updated.

THE EVOLUTION OF TREATMENT PRODUCTS SINCE 1950

2025 – 2030	Anti-antithrombin? Other gene therapies? More anti-TFPIs? Other approaches? Anti-ProteinCs?
2023-24	First anti-TFPIs (concizumab, first approved by Health Canada in 2023, and marstacimab first approved by the U.S. FDA in 2024)
2023	First ultra-extended half-life FVIII (approved by Health Canada in 2025) First FIX gene therapies (first approved by Health Canada and by the European Medicines Agency) First FVIII gene therapy (first approved by the European Medicines Agency)
2018	First FVIII mimetic (emicizumab, first approved by the U.S. FDA)
2014	First extended half-life FVIII and IX concentrates (first approved by Health Canada)
1997	First recombinant FIX concentrate (first approved by the U.S. FDA)
1996	First approval of recombinant FVIIa to treat bleeding in people with inhibitors
1992	First recombinant FVIII concentrate (first approved by the U.S. FDA)
1981	First virally inactivated factor concentrate (FVIII-VWF, first approved in Germany)
1977	Desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease
1970	First FIX concentrate
1966	First FVIII concentrate
1965	Cryoprecipitate for hemophilia A
1950s and 1960s	Fresh frozen plasma, whole blood

N.B. These dates reflect when a major regulator–for example, the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada–first approved the therapy, and not necessarily when it became commercially available.

FROM IDEA TO MEDICINE: THE MANY STEPS TO DRUG APPROVAL

STEPS	DESCRIPTION	TIME REQUIRED
STEP 1 **Discovery and development**	Researchers typically discover new drugs through: ▪ new insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease; ▪ many tests of molecular compounds to find possible beneficial effects against a disease. For example, over 2,400 monoclonal antibodies were tested and modified in the development of emicizumab to find the one that best mimicked factor VIII; ▪ testing existing treatments in a different disease; ▪ new technologies, such as gene therapy. At this stage in the process, thousands of compounds may be potential candidates for development as a medical treatment. After early testing, however, only a small number of compounds look promising and call for further study.	Several years
STEP 2 **Preclinical research**	Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called **toxicity**. The two types of preclinical research are: ▪ in vitro (in a test tube); ▪ in vivo (in a living organism, for example, mice).	Months or years
STEP 3 **Clinical research**	"Clinical research" refers to studies, or trials, that are done in people. As the developers design the clinical study, they consider what they want to accomplish for each of the different clinical research phases. Phase 1: A small number of people to evaluate safety and find the proper dosage. Phase 2: A larger number of people to evaluate effectiveness (efficacy) and side effects. Phase 3: A longer study – one to four years – with even more people to further evaluate effectiveness and monitor adverse reactions.	Phase 1: several months Phase 2: several months Phase 3: 1 to 4 years

STEPS	DESCRIPTION	TIME REQUIRED
STEP 4 **Regulatory review**	If the clinical trials are promising, the drug developer can file an application with the regulator – for example, the U.S. FDA, Europe's EMA or Health Canada – to market the drug. The regulator will look at: ▪ Indications (for whom the drug is intended); ▪ Proposed labeling; ▪ Safety information (adverse events, toxicities); ▪ Effectiveness information; ▪ Patent information; ▪ All data from clinical trials; ▪ Directions for use, including dosage.	6 to 12 months
STEP 5 **Post-marketing drug safety monitoring**	Even though clinical trials provide important information on a drug's effectiveness and safety, it is impossible to have complete information about the safety of a drug at the time of approval. Despite the rigorous steps in the process of drug development, limitations exist. Therefore, the true picture of a product's safety evolves over the years that make up a product's lifetime in the marketplace. Regulators review reports of problems, called adverse events, and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues, including cancelling the market approval and having the drug withdrawn. In many cases, a Phase 4 post-marketing study is conducted, after the drug has been approved and introduced, to collect information from more patients, and validate safety and effectiveness.	Ongoing
STEP 6 **Health technology assessment (HTA)**	Even if national regulators approve a new drug as safe and effective, there is no guarantee it will come to market in a given country. It needs to go through a health technology assessment to evaluate if it as good or better than existing treatments for the disease, and if it is cost-effective. In Canada, recommendations on whether or not to pay for a drug through public drug plans are made by the *Institut national d'excellence en santé et en services sociaux* (INESSS) in Québec and by Canada's Drug Agency (CDA, formerly CADTH) for the other provinces and territories.	6 months

STEPS	DESCRIPTION	TIME REQUIRED
STEP 7 **Price negotiations**	If a drug is recommended by HTA bodies, a price must then be determined. This can happen in different ways. ▪ For most new therapies, the manufacturer negotiates with the pan-Canadian Pharmaceutical Alliance on behalf of all federal, provincial and territorial public drug plans. Each program makes its own decision. This means that a drug may be made available in one jurisdiction but not in another. ▪ For plasma-derived medicinal products such as factor concentrates and alternatives including recombinant FVIII and IX and emicizumab, Canadian Blood Services and Héma-Québec set the prices. This can be through direct negotiations with the manufacturer or through a tender process.	6 months
STEP 8 **A final decision on introducing, and paying for, a new drug**	After all these steps, the thirteen provincial and territorial Ministries of Health make separate and final decisions to reimburse (or not) the manufacturer and make the treatments available. For plasma-derived medicinal products and their alternatives, two decisions on access are made, either by the Québec Ministry of Health, or by the provincial/territorial Ministries of Health for the rest of Canada.	Months or years

Only one out of ten (10%) new drugs make it through these many steps to approval and commercialization. The other nine (90%) fail. Some fail in the Phase 1 clinical trial because they are found to be unsafe. Others fail in Phase 2 because they lack efficacy; they do not do what they are designed to do, or not well enough. Others fail in Phase 3, when the drugs are tested in larger numbers of people, and the results are less promising than in the earlier trials. Some drugs, though they completed the clinical trials, are not approved for use by the regulator. And finally, some drugs are rejected in the health technology stage or by the health ministries because they are not cost-effective or their budget impact is too high.

OVERVIEW OF NOVEL THERAPIES

FACTOR CONCENTRATES

Extended half-life factor (EHL) concentrates were first approved in 2014. Half-life is defined as the time it takes for half (50%) of the active drug to be eliminated from the body.

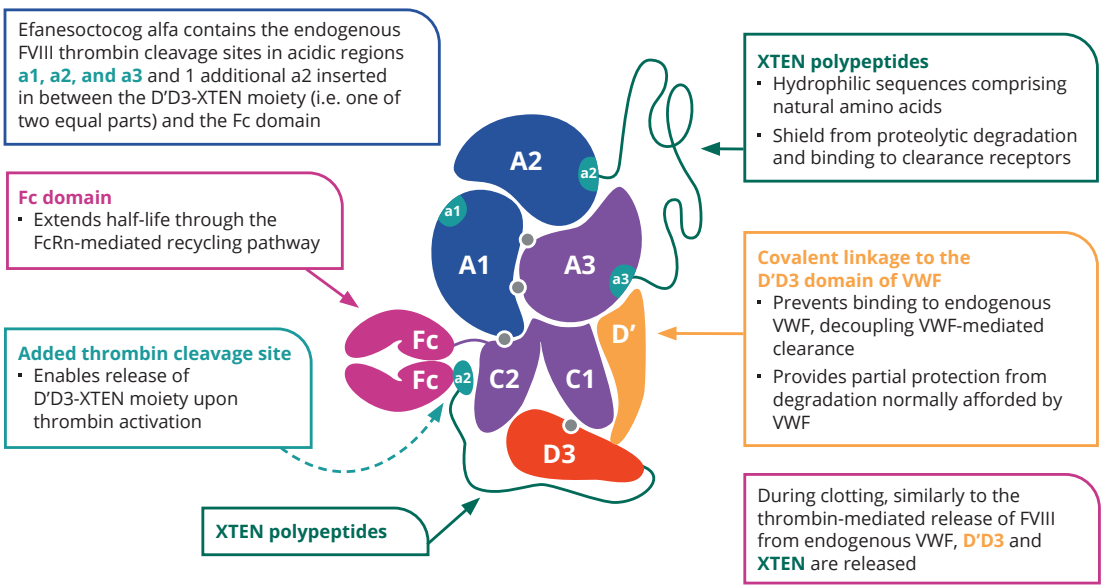
EHL FVIII concentrates extend half-life by about 50% from 12-14 hours to 19-20 hours. This means the frequency of prophylactic infusions can be reduced from three times per week to two times per week for many people with hemophilia A.

EHL FIX concentrates extend half-life by several-fold from 20 hours to close to 100 hours. This means the frequency of prophylactic infusions can be reduced from two times per week to once per week or even less often for many people with hemophilia B.

These EHL concentrates also make it easier to maintain a higher trough level of FVIII or IX. The trough level is the lowest level of factor expression in the body just before the next prophylactic infusion.

In 2023, an ultra-extended half-life FVIII, efanesoctocog alfa or Altuviiio, was approved in the U.S. It extends FVIII half-life to 40 hours. It makes possible once-weekly infusions with trough levels of 15%. See Diagram 1 below. [See **page 16** for more information.]

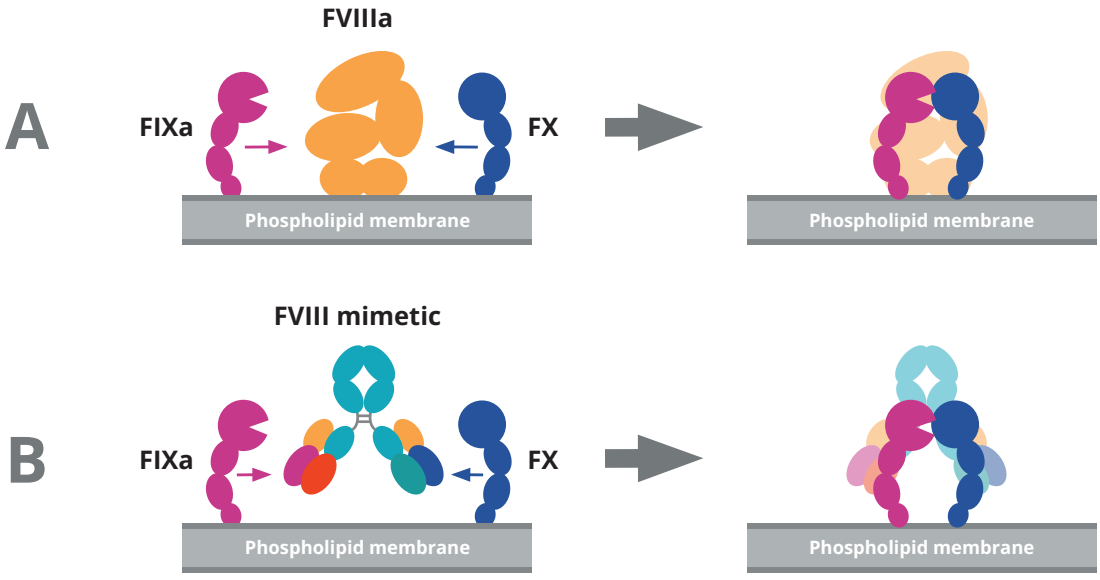
DIAGRAM 1 – EFANESOCTOCOG ALFA



FVIII MIMETICS

In 2018, the first FVIII mimetic, emicizumab, was introduced. It is a bispecific monoclonal antibody that mimics the role of FVIII in the coagulation process. Its two arms bind to FIXa and FX in a way that is similar to natural FVIII. A key difference is that FVIII mimetics are described as constitutively active, meaning that they do not require activation to function in the clotting process. This property allows for more stable and predictable activity, compared to factor VIII concentrates, leading to a more constant effect on the clotting system. On the other hand, natural FVIII has an on/off switch, which must be activated by other clotting factors like thrombin or activated FX before it can participate in the clot formation.

DIAGRAM 2 – FVIII MIMETICS MECHANISM OF ACTION



Because FVIII mimetics are different from natural FVIII, they are not impacted by the presence of antibodies (inhibitors) against FVIII. As a result, they are equally effective prophylactic options to prevent bleeding in people with and without inhibitors to FVIII. Antibodies to FVIII mimetics develop in 1% of people; however, even when they do, the treatment often continues to work well.

Emicizumab is administered subcutaneously (under the skin), not intravenously (into a vein). It has a half-life of 28 days so it can be injected less often—every 7, 14 or 28 days—and people can maintain a constant level of protection against bleeding. This protection is considered to be about the same as a FVIII level of 10-20%. Emicizumab cannot, however, be used to stop breakthrough bleeding. FVIII is required when bleeding occurs and in some surgeries. [See **page 17**]

More potent FVIII mimetics are being developed. One is called denecimig, or Mim8. It is in Phase 3 clinical trials and may soon be approved by regulators. Research results show it generates more thrombin and thus has a higher equivalence in FVIII compared to emicizumab. [See **page 19**]

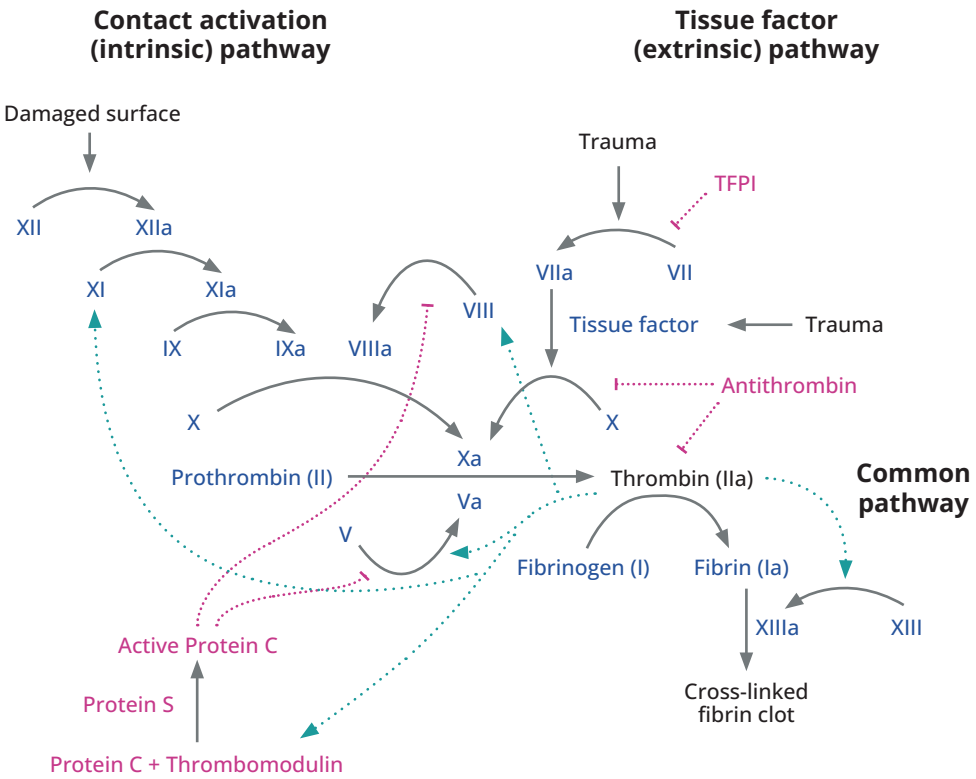
A third FVIII mimetic, called NXT-007, is in early Phase 1/2 clinical trials. It aims to achieve an even higher level of protection against bleeding, possibly in the normal range.

In an entirely novel approach, preclinical work is advancing on a FVIII mimetic that can be taken as a once-daily pill.

REBALANCING AGENTS

The human coagulation system is complex. It includes compounds that promote coagulation, called procoagulants. These include the clotting factors such as factors I, II, V, VII, VIII, IX, X, XI, XIII and von Willebrand factor (VWF). It also includes compounds that inhibit, or discourage, coagulation, called anticoagulants. These include antithrombin, anti-ProteinC, anti-ProteinS and anti-tissue-factor-pathway inhibitors (anti-TFPIs). See Diagram 3.

DIAGRAM 3 – THE COAGULATION CASCADE

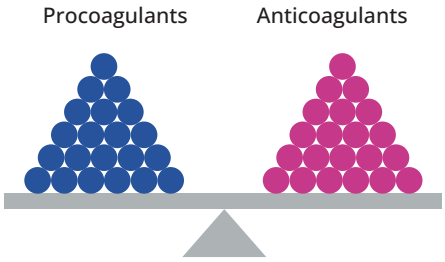


In a person with normal coagulation, the procoagulants (in blue) and the anticoagulants (in pink) are in balance. People make clots when there is an injury to a blood vessel, but they do not make clots when they do not need to, for example, an undesired blood clot in a vein or an artery. This clot can cause heart attacks, strokes, deep vein thrombosis and pulmonary embolisms.

The coagulation systems of people with bleeding disorders are not in balance. They do not have enough of the procoagulants. So a new approach is to try to rebalance coagulation, not by adding procoagulants such as factors VIII or IX as has been done for decades, but rather by decreasing the anticoagulants. See Diagram 4.

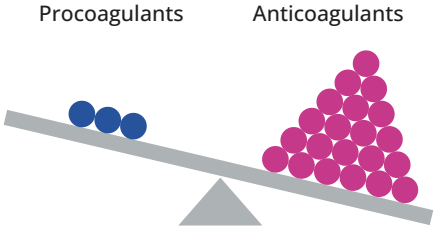
DIAGRAM 4 – THE IDEA BEHIND REBALANCING AGENTS

A **Normal hemostatic balance**



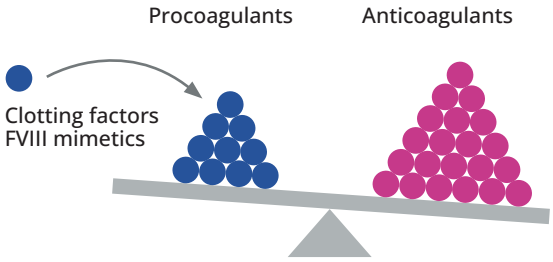
In Part A, the coagulation system is normal and in balance.

B **People with bleeding disorders**



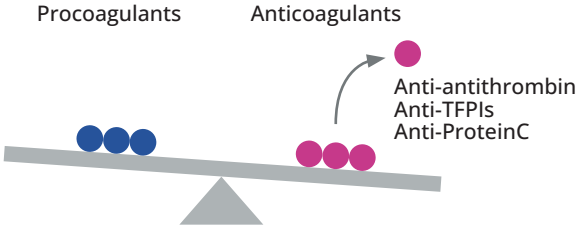
Part B represents a person with a bleeding disorder. The natural procoagulants (for example, clotting factors) are lacking and there is abnormal bleeding.

C **Treatment with procoagulants**



In Part C, procoagulants (for example, clotting factors or FVIII mimetics) are added and coagulation improves.

D **Treatment with less anticoagulants**



In Part D, rather than adding procoagulants, anticoagulants (for example, fitusiran, anti-TFPIs, Protein C inhibitor or Protein S inhibitor) are removed and coagulation is somewhat rebalanced.

In simpler terms:

- Too little procoagulant: abnormal, excessive bleeding;
- Too much procoagulant: abnormal, excessive clotting;
- Too little anticoagulant: abnormal, excessive clotting;
- Too much anticoagulant: Abnormal, excessive bleeding.

There are currently several rebalancing agents being developed:

- Anti-TFPIs like concizumab and marstacimab; [See **page 21**]
- Anti-antithrombin like fitusiran; [See **page 23**]
- A Protein S inhibitor like VGA039. [See **page 25**]

While early clinical trials for rebalancing agents included only people with hemophilia A and B, with and without inhibitors to FVIII and IX, these rebalancing agents could, in theory, prevent bleeding in a wide range of inherited bleeding disorders. Future research will measure this potential.

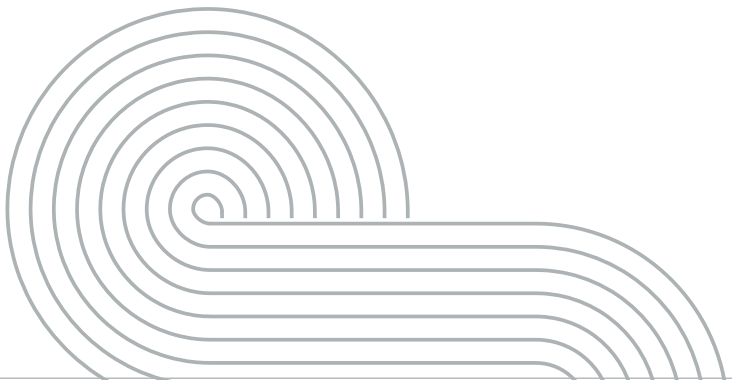
GENE THERAPIES

See the Canadian Hemophilia Society Gene Therapy Education Program at **www.hemophilia.ca/gene-therapy**. It includes a comprehensive booklet entitled *All About Hemophilia Gene Therapy*, a series of podcasts with Canadian and international experts and timely webinars.

OTHER NOVEL APPROACHES

These include:

- a bispecific antibody to treat Glanzmann thrombasthenia; [See **page 27**]
- a Protein S inhibitor like VGA039 to treat von Willebrand disease (VWD). [See **page 25**]



KEY QUESTIONS TO ASK

These are some of the key questions to ask when you discuss treatment options with your health care providers.

- How long has the treatment been in regular use?
- Is the treatment ...
    1. a prophylactic therapy (a prophylactic treatment is taken on a routine schedule to prevent bleeding)?
    2. a therapy to stop active bleeding (on-demand)?
    3. both?
- How is the treatment administered:
    1. intravenously?
    2. subcutaneously?
    3. orally (a pill)?
    4. in some other way?
- Can the treatment be administered at home? How easy is the treatment to administer? How long does it take?
- Does the product need to be refrigerated? How long can it be at room temperature?
- How long does the treatment work:
    1. a few hours like rFVIIa?
    2. a few days like many factor concentrates?
    3. a few weeks like emicizumab?
    4. years like gene therapy?

- How well does the treatment work?
  - How quickly does it stop bleeding?
  - Is it used for prevention of bleeding (prophylaxis) only, or can it be used to treat bleeding too?
  - How many bleeds does a person have in a year, on average, if on prophylaxis?
  - What physical activities might a person be able to do when on this treatment?
- What safety concerns or complications have been reported?
  - Are there any side effects to be aware of?
  - Were there any issues with unusual blood clots (venous or arterial thrombosis) while on treatment? How did they happen? How were they treated?
  - Are there therapies that should be avoided while on this treatment?
- Is there any additional monitoring or follow-up if a person switches treatments?
- Are there any limitations on who can receive the treatment? Age limits? Disease severity? Other medical conditions that would stop someone from receiving this treatment?

Altuviiio in Canada and the U.S. (Altuvoct in Europe)**, (efanesoctocog alfa) Sanofi**

APPROVED INDICATIONS (CANADA)

For children and adults with hemophilia A, all ages.

- Routine prophylaxis to reduce the frequency of bleeding episodes;
- On-demand treatment and control of bleeding episodes;
- Perioperative management of bleeding.

ACCESS STATUS

- Approved by the U.S FDA and by Europe's EMA in 2024, and by Health Canada in March 2025.
- Positive health technology assessments issued by both CDA and INESSS in summer 2025.
- Availability expected in Canada in mid-2026.

MECHANISM OF ACTION

Efanesoctocog alfa is an ultra-extended half-life recombinant FVIII. It is infused intravenously. Its half-life is approximately 40 hours, compared to 12-14 hours for standard half-life FVIIIs and 18-20 hours for other extended half-life FVIIIs.

To extend half-life, efanesoctocog alfa connects three components to the FVIII molecule:

- Fc fusion to help FVIII recirculate;
- XTEN technology to shield FVIII from breaking down; and
- von Willebrand factor fragments to keep FVIII in the bloodstream longer.

RESEARCH RESULTS*

Results from a Phase 3 trial with 149 people:

- Average annual bleeding rate of 0.71 (lower than rates with prior FVIII prophylaxis);
- In adolescents and adults, after a dose of 50 IUs/kg once a week, average FVIII level of 40% after 4 days, and 15% after 7 days;
- In children under 12 years, after a dose of 50 IUs/kg once a week, an average FVIII level of 40% for 2 to 3 days, and 10% after 7 days;
- 97% of bleeds resolved with one injection of efanesoctocog alfa;
- Improvements in physical health, pain intensity and joint health;
- No new inhibitors;
- Acceptable side effect profile.

ADVANTAGES

- Capacity to achieve better bleed protection because of extended half-life, compared to other FVIII concentrates and FVIII mimetics.
- Capacity to achieve higher trough level compared to other FVIIIs.
- Potential for better protection from bleeding during riskier activities (for example, contact sports).
- Potential to match infusions with period of highest risk.
- No need to combine with a second treatment product as may be necessary with a FVIII mimetic or rebalancing agent in the event of breakthrough bleeding.

DISADVANTAGES

- Requires IV infusion (whereas FVIII mimetics are injected subcutaneously).
- Requires weekly infusion (whereas FVIII mimetics can be injected every 1, 2 or 4 weeks).

REFERENCES* **Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A.** Published January 25, 2023. N Engl J Med 2023;388:310-318. DOI: 10.1056/NEJMoa2209226

Emicizumab (Hemlibra), Roche

APPROVED INDICATIONS (CANADA)	ACCESS STATUS
People with hemophilia A, with and without inhibitors, all ages ▪ Routine prophylaxis to prevent bleeding. N.B. 1. Emicizumab cannot be used to treat active bleeding. In these cases, FVIII is required. 2. There is limited clinical experience of use in people with mild or moderate hemophilia A.	▪ Approved by Health Canada for hemophilia A with inhibitors in 2018. ▪ Approved by Health Canada for hemophilia A without inhibitors in 2019. ▪ Available in Canada for those with severe hemophilia A and those with mild/moderate hemophilia A with a severe bleeding phenotype.

MECHANISM OF ACTION

Hemlibra is a bispecific antibody designed to mimic the function of factor VIII and bring together activated factor IX and factor X to continue the natural coagulation cascade and help restore the blood clotting process for hemophilia A. [See Diagrams 2 and 3 on **pages 10 and 11**.]
It is injected subcutaneously (under the skin).

RESEARCH RESULTS*

HAVEN 1 in 109 adolescents and adults with inhibitors:
- 87% reduction in bleeds compared to no prophylaxis;
- 79% reduction in bleeds compared to prior prophylaxis with bypassing agents;
- 62% of people had no bleeds during an average of 25 weeks of observation.

HAVEN 2 in 59 children less than 12 years with inhibitors:
- 86% of people had no bleeds during an average of 29 weeks of observation.

HAVEN 3 in 152 adolescents and adults without inhibitors:
- 96% reduction in bleeds compared to no prophylaxis;
- 68% reduction in bleeds compared to prior prophylaxis with FVIII;
- 55% of people had no bleeds during an average of 24 weeks of observation.

More than 25,000 people are now treated with emicizumab worldwide. Health authorities no longer require special expedited safety reporting for thromboembolic events (TEs) and thrombotic microangiopathies (TMAs) for emicizumab; however, monitoring and reporting of safety data are ongoing, with no new safety signals found to date. Note that there are warnings about the use of activated prothrombin complex concentrate (FEIBA) at the same time as emicizumab following thrombotic events in those with inhibitors.

Emicizumab (Hemlibra), Roche

ADVANTAGES	DISADVANTAGES
▪ Excellent protection from bleeding compared to prior prophylaxis with FVIII. ▪ Constant level of protection equivalent to FVIII levels of 10-20%. ▪ No troughs in protection, as with FVIII prophylaxis. ▪ Subcutaneous injection every 7, 14 or 28 days.	▪ Emiczumab cannot be used to treat active bleeding; FVIII or rFVIIa are required in these cases. ▪ Protection from bleeding may not be sufficient for high-risk activities; FVIII may be required. ▪ Patients/caregivers may lose their IV infusion skills. ▪ Patients may need to go to the clinic or ED when FVIII is needed.

REFERENCES* **Emicizumab Prophylaxis in Hemophilia A with Inhibitors.** Published August 31, 2017. N Engl J Med 2017;377:809-818, DOI: 10.1056/NEJMoa1703068

Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. Published August 29, 2018. N Engl J Med 2018;379:811-822. DOI:10.1056/NEJMoa1803550

A multicenter, open-label Phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors
Emicizumab Prophylaxis in People with Haemophilia A: Summary of 10 Years of Safety Data on Thromboembolic Events and Thrombotic Microangiopathy. Published date 06 February, 2024

Denecimig (Mim8), Novo Nordisk

PROPOSED INDICATIONS	ACCESS STATUS
People with hemophilia A, with and without inhibitors, all ages ▪ Routine prophylaxis to prevent bleeding. N.B. Mim8 cannot be used to treat active bleeding. In these cases, FVIII is required.	▪ Phase 3 clinical trials in 300 children and adults with and without inhibitors have demonstrated safety and efficacy. In September 2025, Novo Nordisk submitted Mim8 for review by the U.S. FDA.

MECHANISM OF ACTION

Mim8 (denecimig) is a fully human bispecific IgG4 antibody that mimics the function of activated FVIII (FVIIIa) by bridging activated FIXa and FX, enhancing the proteolytic activity of FIXa and enabling effective activation of FX. [See Diagrams 2 and 3 on **pages 10 and 11**.]

The modes of action of Mim8 and emicizumab are similar, but there are differences in their respective anti-FIXa and anti-FX arms that affect their FVIIIa-like function. It is injected subcutaneously (under the skin).

RESEARCH RESULTS*

Two Phase 3 studies are currently underway to evaluate the efficacy and safety of Mim8, FRONTIER2, a global study in patients with hemophilia A with or without inhibitors, to demonstrate the hemostatic effect of Mim8 dosed once weekly and once monthly as bleeding prophylaxis, and FRONTIER3 a global study investigating the safety of Mim8 in young patients with hemophilia A (aged 1-11 years) with or without inhibitors.

The FRONTIER 2 study enrolled over 250 adolescents and adults aged 12 to 64, with and without inhibitors:

- There were no thrombotic events;
- There were no serious adverse events related to the drug;
- 5-12% had injection site reactions;
- Three people withdrew from the study;
- The plasma concentration of Mim8 is 10 times lower than emicizumab but achieves 3 times higher thrombin generation and an average FVIII equivalence of 42%, compared to 14% with emicizumab;
- Phase 3 results show a 43-48% reduction in ABR compared to previous prophylaxis;
- 65% of people had no bleeds in a 26-week period.

ADVANTAGES	DISADVANTAGES
▪ Like emicizumab, Mim8 is injected subcutaneously every 1, 2 or potentially 4 weeks. ▪ Mim8 demonstrates higher thrombin generation compared to emicizumab and therefore potentially better bleed prevention, though this has yet to be shown in long-term clinical studies.	▪ Mim8 cannot be used to treat active bleeding; FVIII or rFVIIa are required in these cases. ▪ Protection from bleeding FVIII may not be sufficient for high-risk activities; FVIII may be required. ▪ Patients/caregivers may lose their IV infusion skills. ▪ Patients may need to go to the clinic or ED when FVIII is needed.

REFERENCES* **FRONTIER1: a partially randomized Phase 2 study assessing the safety, pharmacokinetics, and pharmacodynamics of Mim8, a factor VIIIa mimetic.** Journal of Hemostasis and Thrombosis, Volume 22, Issue 4.

Concizumab (Alhemo), Novo Nordisk

APPROVED INDICATIONS (CANADA)	ACCESS STATUS
Adolescents and adults with hemophilia A or B, with inhibitors to FVIII or FIX.	▪ Concizumab was approved by Health Canada for people with hemophilia B with inhibitors in March 2023 and for those with hemophilia A with inhibitors in August 2023, and by the U.S. FDA in December 2024. ▪ Concizumab has not undergone a health technology assessment by either CDA or INESSS, and is not currently available in Canada. The manufacturer announced in late 2024 that it will not market concizumab in Canada in the foreseeable future.

MECHANISM OF ACTION

Concizumab is a rebalancing agent. [See **page 11**]

The monoclonal antibody in concizumab recognizes a protein, Tissue Factor Pathway Inhibitor or TFPI, that prevents or downregulates clotting. By binding to this protein, concizumab allows clotting to improve and prevent bleeding in people with hemophilia with inhibitors. It is injected subcutaneously (under the skin).

RESEARCH RESULTS*

The explorer7 and explorer8 trials studied 76 adolescents and adults with hemophilia A with inhibitors, 50 with hemophilia B with inhibitors, 80 with hemophilia A without inhibitors, and 64 with hemophilia B without inhibitors over 56 weeks. Average annual treated bleed rates for the four groups were between 0.7 and 2.8. Breakthrough bleeds were treated with factor concentrates, most with a single infusion.

Five non-fatal thrombotic events (2 arterial and 3 venous) occurred in three patients in the early part of the trials. All three patients had risk factors for thrombosis. The trials were paused. Risk reduction strategies were introduced, including guidelines on the use of factor concentrates. There were no thrombotic events after the trials restarted.

Concizumab (Alhemo), Novo Nordisk

ADVANTAGES	DISADVANTAGES
▪ Subcutaneous injection (1-3 mL) in a pre-filled pen. ▪ Low annual bleeding rates. ▪ Adjustable dose based on personal levels.	▪ Daily injection. ▪ Concizumab cannot be used to treat active bleeding; FVIII or FIX are required in these cases. ▪ Protection from bleeding may not be sufficient for high-risk activities; FVIII or FIX may be required. ▪ Patients/caregivers may lose their IV infusion skills. ▪ Patients may need to go to the clinic or ED when FVIII is needed. ▪ It is recommended to pause Alhemo before major surgery and resume 10-14 days later. ▪ There is risk of thrombosis, especially for those at higher risk for thromboembolic events. ▪ There is low risk of neutralizing anti-drug antibodies

REFERENCES* **Concizumab efficacy results at 56-week cut-off in patients with haemophilia A/B without inhibitors: an intra-patient analysis from the Phase 3 explorer8 study** (OC 40.4, ISTH 2024). Lancet Haematol. 2024 Dec;11(12):e891-e904. doi: 10.1016/S2352-3026(24)00307-7. Epub 2024 Nov 6.

Marstacimab (Hympavzi in the U.S.), Pfizer

APPROVED INDICATIONS (U.S.)

Routine prophylaxis to prevent or reduce bleeding in adolescents, ages 12 and older, and adults with hemophilia A or B, without inhibitors to FVIII or FIX.

ACCESS STATUS

- Marstacimab was approved by the U.S. FDA and by the European EMA in late 2024 for routine prophylaxis to prevent or reduce bleeding in adolescents, ages 12 and older, and adults with hemophilia A or B, without inhibitors to FVIII or FIX.
- Marstacimab is not under review by Health Canada. The manufacturer has announced that it will gather more data before submitting a request for market authorization from Health Canada. The health technology assessments could begin then.

MECHANISM OF ACTION

Marstacimab is a rebalancing agent. [See **page 11**]

Marstacimab targets an anticoagulant protein known as tissue factor pathway inhibitor (TFPI). It works by blocking and effectively preventing TFPI from performing the anticoagulant function that it naturally carries out in the human body. It is injected subcutaneously (under the skin).

RESEARCH RESULTS*

The BASIS Phase 3 trial studied 20 adolescents and 108 adults with severe or moderately severe hemophilia A or B, without inhibitors for 12 months.

People treated with marstacimab showed a 5.08 annual bleed rate compared to 7.85 while on previous routine prophylaxis. This is considered "non-inferior."

Low-titer anti-drug antibodies developed in 23 people; 22 had resolved by the end of the study.

No thromboembolic adverse events occurred, though the FDA label comes with warnings and precautions about circulating blood clots (thromboembolic events) and hypersensitivity.

ADVANTAGES

- Subcutaneous injection in a pre-filled syringe.
- Weekly injection.
- Annual bleeding rates similar to routine prophylaxis with factor concentrates.
- Adjustable dose based on personal levels.

DISADVANTAGES

- Marstacimab cannot be used to treat active bleeding; FVIII or FIX are required in these cases.
- Protection from bleeding may not be sufficient for high-risk activities; FVIII or FIX may be required.
- Patients/caregivers may lose their IV infusion skills.
- Patients may need to go to the clinic or ED when FVIII or FIX is needed.
- Risk of thrombosis, especially for those at higher risk for thromboembolic events.
- Low risk of neutralizing anti-drug antibodies.
- Marstacimab must be discontinued before major surgery.

REFERENCES* Matino D, Acharya S, Palladino A, et al. **Efficacy and Safety of the Anti-Tissue Factor Pathway Inhibitor Marstacimab in Participants with Severe Hemophilia without Inhibitors: Results from the Phase 3 Basis Trial.** Blood, Volume 142, issue Supplement 1, November 2, 2023

Fitusiran, Sanofi

PROPOSED INDICATIONS	ACCESS STATUS
Routine prophylaxis to prevent or reduce bleeding in adolescents, ages 12 and older, and adults with hemophilia A or B, with or without inhibitors to FVIII or FIX.	▪ Fitusiran was granted a marketing authorization from the U.S. FDA in March 2025 as routine prophylaxis to prevent or reduce bleeding in adolescents, ages 12 and older, and adults with hemophilia A or B, with or without inhibitors to FVIII or FIX.

MECHANISM OF ACTION

Fitusiran is a rebalancing agent. [See **page 11**]

Fitusiran is a subcutaneous investigational small interfering RNA therapeutic, which reduces antithrombin levels with the goal of rebalancing haemostasis in people with hemophilia A or B, regardless of inhibitor status. It is injected subcutaneously (under the skin).

RESEARCH RESULTS*

The ATLAS-PPX trial studied 65 people with hemophilia A or B, with and without inhibitors who had been in previous prophylaxis for 6 months with bypassing agents (for those with inhibitors) or clotting factor concentrates (for those without) and then on fitusiran for six months.

Average annual bleeding rates were reduced by 80% in those previously receiving bypassing agent prophylaxis and 46% in those on FVIII or FIX prophylaxis. 63% experienced no bleeds versus 17% on clotting factors.

Two participants (3.0%) experienced suspected or confirmed thromboembolic events with fitusiran. Following this, to mitigate the risk of thrombosis, a revised antithrombin-based dose regimen was developed. It keeps antithrombin levels at 15-35% of normal.

ADVANTAGES	DISADVANTAGES
▪ Subcutaneous injection in a pre-filled syringe. ▪ Weekly injection. ▪ Annual bleeding rates comparable to routine prophylaxis with factor concentrates. ▪ Adjustable dose based on personal levels.	▪ Fitusiran cannot be used to treat active bleeding; FVIII or FIX are required in these cases. ▪ Protection from bleeding may not be sufficient for high-risk activities; FVIII or FIX may be required. ▪ Patients/caregivers may lose their IV infusion skills. ▪ Patients may need to go to the clinic or ED when FVIII or FIX is needed. ▪ There is risk of thrombosis, especially for those at higher risk for thromboembolic events. ▪ There is low risk of neutralizing anti-drug antibodies.

REFERENCES* **Fitusiran prophylaxis in people with hemophilia A or B who switched from prior BPA/CFC prophylaxis: the ATLAS-PPX trial.** Blood, Volume 143, Issue 22. May 30, 2024

ATLAS OLE Incidence of thrombotic events in the fitusiran clinical development program: Fitusiran prophylaxis under an AT-DR led to a marked reduction in TEs with substantially greater exposure on the AT-DR (oral presentation, ISTH 2024 OC40.2).

Hepatobiliary events in the fitusiran clinical development program with the revised AT-based dose regimen: Fitusiran prophylaxis under an AT-DR led to reductions in liver transaminase elevations and cholecystitis/cholelithiasis events. Liver transaminase elevations were infrequent and transient, and events of cholecystitis/cholelithiasis resolved without clinical complications with no fitusiran dose interruptions or discontinuations (poster ISTH 2024, OC40.3).

SerpinPC, Centessa Pharmaceuticals

PROPOSED INDICATIONS	ACCESS STATUS
Routine prophylaxis to prevent or reduce bleeding in people with hemophilia A or B, without inhibitors to FVIII or FIX.	Serpin PC was in a Phase 1/2 clinical study; however, in late 2024, the manufacturer announced it was halting development to focus its resources on other pipeline products. At this time, it is not known if the rights to SerpinPC might be purchased by another company to allow clinical research to continue.

MECHANISM OF ACTION

SerpinPC is a rebalancing agent. [See **page 11**]

SerpinPC is an investigational serine protease inhibitor (SERPIN) engineered to specifically inhibit Activated Protein C (APC). It is injected subcutaneously (under the skin).

RESEARCH RESULTS*

AP-0101 investigated the safety, tolerability, pharmacokinetics and efficacy of SerpinPC in subjects with severe hemophilia A and B.

Part 1a was a Single Ascending Dose Study of SerpinPC in 15 healthy male volunteers and 12 males with severe hemophilia.

Part 2 enrolled 23 males with severe hemophilia (19 hemophilia A and 4 hemophilia B), who were not on replacement factor prophylaxis, to receive SerpinPC at three different doses: 0.3, 0.6 or 1.2 mg/kg. It was administered as a subcutaneous injection once every 4 weeks over a 24-week period (6 total doses).

In Part 3, subjects who completed Part 2 received a flat dose of 60 mg of SerpinPC once every 4 weeks for 48 weeks.

Part 4 was a further extension in which subjects who completed Part 3 received 1.2 mg/kg of SerpinPC once every 2 weeks for 24 weeks.

Part 5 was a further extension in which subjects who completed Part 4 continued to receive 1.2 mg/kg of SerpinPC once every 2 weeks for 52 weeks.

Results—annualized bleed rates, safety and tolerability, including available pharmacokinetic and anti-drug antibody data—are not yet publicly available.

ADVANTAGES	DISADVANTAGES
	▪ Phase 3 results are needed to be able to compare SerpinPC with other treatments.

VGA039, Star Therapeutics

PROPOSED INDICATIONS	ACCESS STATUS
Routine prophylaxis to prevent or reduce bleeding in people with von Willebrand disease and, potentially other inherited bleeding disorders.	VGA039 is in early Phase 1 clinical trials. In January 2025, the U.S. FDA granted Fast Track designation. This designation aims to facilitate the development and expedite the review of medicines that demonstrate the potential to treat serious conditions and fill an unmet medical need.

MECHANISM OF ACTION

VGA039 is a subcutaneously delivered monoclonal antibody therapy designed to target Protein S as a means of restoring proper blood clotting in people with all types of von Willebrand disease (VWD). Protein S functions with other proteins in the body to prevent excessive blood clotting.

RESEARCH RESULTS*

Interim clinical data, based on just three VWD patients, one with type 2M and two with type 3, showed that a subcutaneous dose of VGA039 was associated with substantial (75% to 88%) reductions in annualized bleed rates in the three patients.

ADVANTAGES	DISADVANTAGES
▪ This therapy is first targeted at people with VWD. Only later will its potential to treat other inherited bleeding disorders be explored.	▪ Clinical trials are in their very early stages.

GENE THERAPIES

In the past few years, we have started to see promising results from the late stages of clinical trials for gene therapy in both hemophilia A and B. With these results, however, we have learned that the reality of gene therapy differs from original hopes and expectations. The gene therapies that will be made available are promising new treatment options but are not full cures and are not for everyone. Gene therapy is very different from the prophylaxis therapies we are used to. It is a one-time treatment that cannot be taken back and cannot be repeated. And we have also learned that we have a lot of work to do to ensure its safe and optimal introduction as a treatment option.

To keep the community informed about gene therapy, its benefits and risks, what we know and don't know, and what questions we need to continue to try answering, the Canadian Hemophilia Society created its Gene Therapy Education Program. It includes a comprehensive booklet entitled *All About Hemophilia Gene Therapy*, a series of podcasts with Canadian and international experts and timely webinars. All is available at **www.hemophilia.ca/gene-therapy**.

OTHER INNOVATIVE THERAPIES IN EARLY CLINICAL TRIALS

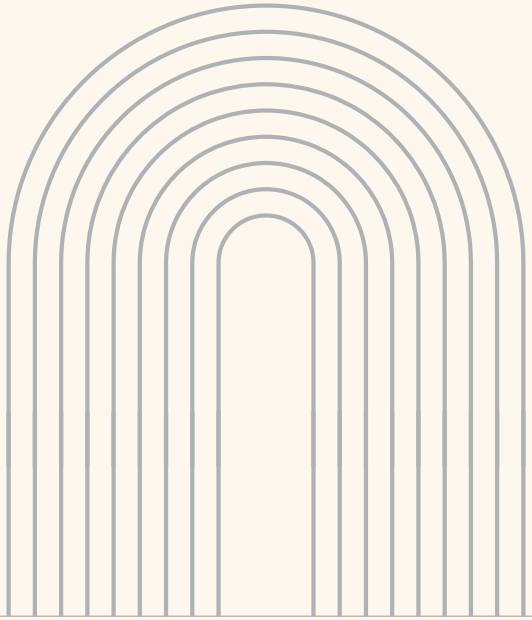
NAME OF THERAPY	TREATMENT INDICATION	MECHANISM OF ACTION	EARLY RESULTS
HMB-001 (Hemab Therapeutics)	Glanzmann thrombasthenia (GT)	HMB-001 is a bispecific antibody to prevent or reduce the frequency of bleeding episodes in patients with GT. HMB-001 works by binding to a membrane protein and accumulating endogenous activated coagulation factor VII (FVIIa) and targeting it to the surface of activated platelets at the site of vascular injury.	▪ In a Phase 1/2 study; ▪ Infrequent, subcutaneous dosing; ▪ No reported treatment-related adverse events; ▪ Initial safety, tolerability, pharmacodynamics and pharmacokinetics results from part A of the Phase 1/2 study are encouraging and support the further development of HMB-001 as a potential prophylactic treatment for GT.

FINAL WORD

While innovation is accelerating, and there are many therapies in clinical development to treat bleeding disorders, it is important to remember that many of these new treatments will not make it to the "finish line," that is, to the patient. There are multiple reasons why an innovative idea will not fulfill its promise. These include:

- The therapy does not work as well as initially hoped.
- There are safety concerns.
- Other treatments are more effective.
- The therapy is not cost-effective compared to existing treatments.
- The manufacturer stops development to redirect resources to other treatments or conditions.
- The pharmaceutical company decides not to market the treatment in Canada.

Some novel therapies, however, will become a reality in coming years and will improve care and treatment. This booklet will be updated regularly to follow their progress. Stay tuned!



ANNEX 1: LIST OF TREATMENT PRODUCTS, TARGETED INDICATIONS AND DEVELOPMENT STAGES

TREATMENT PRODUCT	TARGETED INDICATIONS	DEVELOPMENT STAGE
Efanesoctocog alfa, Altuviiio in the U.S., previously BIVV001	Prophylaxis, on-demand treatment, surgery in people with hemophilia A without inhibitors, all ages, all severities [See **page 16**]	Approved by the U.S FDA and by Europe's EMA in 2024. Approved by Health Canada in March 2025; health technology assessments underway. Availability expected in Canada in early 2026.
Emicizumab (Hemlibra)	Routine prophylaxis to prevent bleeding in people with severe hemophilia A, or moderate hemophilia A with a severe bleeding phenotype, with and without inhibitors, all ages [See **page 17**]	Available across Canada. Not funded for mild and moderate hemophilia A (unless the bleeding phenotype is severe).
Denecimig (Mim8)	Routine prophylaxis to prevent bleeding in people with hemophilia A, with and without inhibitors, all ages [See **page 19**]	Application for a marketing authorization from the U.S. FDA submitted in September 2025, decision expected in early 2026. No announced timetable for Canada.
Concizumab (Alhemo)	Routine prophylaxis to prevent bleeding in people with hemophilia A and B, with and without inhibitors, all ages [See **page 20**]	Approved by Health Canada and U.S. FDA for people with hemophilia A and B, with inhibitors, 12 years and older. Not marketed in Canada.

TREATMENT PRODUCT	TARGETED INDICATIONS	DEVELOPMENT STAGE
Marstacimab (Hympavzi)	Routine prophylaxis to prevent bleeding in people with hemophilia A and B, with and without inhibitors, all ages [See **page 22**]	Approved by U.S. FDA for people with hemophilia A and B, without inhibitors, 12 years and older. Not currently under review by Health Canada.
Fitusiran	Routine prophylaxis to prevent bleeding in people with hemophilia A and B, with and without inhibitors, all ages [See **page 23**]	Approved by U.S. FDA in March 2025. No announced timetable for Canada.
SerpinPC	Routine prophylaxis to prevent bleeding in people with hemophilia A and B, with and without inhibitors, all ages [See **page 24**]	No longer under development by the manufacturer.
VGA039	Routine prophylaxis to restoring proper blood clotting in people with all types of von Willebrand disease (VWD) [See **page 25**]	In Phase 1 clinical trials

ANNEX 2: OTHER RESOURCES

The Canadian Hemophilia Society Gene Therapy Education Program includes a comprehensive booklet entitled *All About Hemophilia Gene Therapy*, a series of podcasts with Canadian and international experts and timely webinars.

www.hemophilia.ca/gene-therapy

The World Federation of Hemophilia (WFH) Shared Decision Making for Hemophilia Treatment Workbook is for people with hemophilia A or B and their health care team. It defines the best practice for shared decision-making in hemophilia treatment and care, and provides a guide for people with hemophilia, caregivers, and healthcare professionals to facilitate successful shared decision-making.

https://elearning.wfh.org/resource/wfh-shared-decision-making-workbook-for-hemophilia-treatment

ANNEX 3: GLOSSARY

Annual bleeding rate – (ABR) the number of bleeds experienced by a person in one year. These could be subcategorized as all bleeds, joint bleeds, traumatic bleeds, bleeds requiring treatment.

Anticoagulant – a substance that has the effect of slowing or inhibiting blood coagulation. Substances can be natural such as antithrombin, or medicinal such as warfarin.

Antithrombin – a small natural glycoprotein that inactivates several enzymes of the coagulation system, inhibiting coagulation

Bispecific monoclonal antibody – an artificial protein that can simultaneously bind to two different types of antigen or two different epitopes, for example emicizumab.

Coagulation cascade – a series of steps in response to bleeding caused by tissue injury, where each step activates the next and ultimately produces a blood clot.

Concizumab – a monoclonal antibody that recognizes a protein, Tissue Factor Pathway Inhibitor or TFPI, to rebalance hemostasis.

Cryoprecipitate – a portion of plasma that is rich in certain clotting factors, notably FVIII and von Willebrand factor.

Denecimig – a bispecific monoclonal antibody that mimics the role of FVIII in the coagulation process. Its two arms bind to FIXa and FX in a way that is similar to natural FVIII.

Desmopressin – a hormone that is normally produced in the body to help balance the amount of water and salt. It can aid coagulation in certain types of hemophilia A and von Willebrand disease.

Efanesoctocog alfa – an ultra-extended half-life recombinant FVIII. To extend half-life, efanesoctocog alfa connects three components to the FVIII molecule: Fc fusion to help FVIII recirculate, XTEN technology to shield FVIII from breaking down, and von Willebrand factor fragments to keep FVIII in the bloodstream longer.

Emicizumab – a bispecific monoclonal antibody that mimics the role of FVIII in the coagulation process. Its two arms bind to FIXa and FX in a way that is similar to natural FVIII.

Fc fusion – a process whereby an Fc domain of an antibody is covalently linked to another protein, for example FVIII, in this case to extend the half-life of the protein.

Fitusiran – a subcutaneous small interfering RNA therapeutic, which reduces antithrombin levels with the goal of rebalancing hemostasis in people with hemophilia A or B.

FVIII mimetic – a bispecific monoclonal antibody that mimics the role of FVIII in the coagulation process. Its two arms bind to FIXa and FX in a way that is similar to natural FVIII. Examples are emicizumab and denecimig.

Half-life – the time required for a quantity (such as a medicine) to reduce to half of its initial value (and be removed from the body). This can be measured in hours or days for factor concentrates and in days or weeks for FVIII mimetics and rebalancing agents.

Hemostatic balance – the state in which procoagulant and anticoagulant factors are equilibrium with each other, providing normal clotting at the site of a vascular injury.

Indication – the medical condition targeted by a therapy, for example, hemophilia A with FVIII inhibitors.

Intravenous administration – administration of a therapy by infusion into a vein.

In vitro study – "in glass"; a study conducted using components of an organism that have been isolated from their usual biological surroundings, such as micro-organisms, cells, or biological molecules.

In vivo study – "within the living"; a study in which the effects of various biological entities are tested on whole, living organisms or cells, usually animals, including humans.

Marstacimab – a monoclonal antibody that recognizes a protein, Tissue Factor Pathway Inhibitor or TFPI, to rebalance hemostasis.

Monoclonal antibody – (mAb) a man-made protein that acts like a human antibody in the immune system.

Oral administration – administration of a therapy by mouth.

Pharmacodynamics – the body's biological response to a drug.

Procoagulant – a substance that promotes coagulation, for example, clotting factors, fibrinogen and thrombin.

Prophylaxis – a treatment that aims to prevent disease or disease symptoms.

Rebalancing agent – a therapy that restores the balance between procoagulants and anticoagulants to promote normal hemostasis.

Serine protease inhibitor – a compound that interferes with the ability of certain enzymes to break down proteins.

SerpinPC – a serine protease inhibitor (SERPIN) engineered to specifically inhibit Activated Protein C (APC).

Small interfering RNA therapeutic – RNA interference (RNAi) is an ancient biological mechanism used to defend against external invasion. It theoretically can silence any disease-related genes in a sequence-specific manner, making small interfering RNA (siRNA) a promising therapeutic modality.

Subcutaneous administration – administration of a therapy by a subcutaneous (under the skin) injection.

Thrombin – the last enzyme in the coagulation cascade, with the function of cleaving fibrinogen to fibrin, which forms the fibrin clot of a hemostatic plug.

Thromboembolic events – a circulating blood clot that gets stuck and causes an obstruction.

Thrombotic microangiopathy – a clinical syndrome defined by the presence of hemolytic anemia (destruction of red blood cells), low platelets, and organ damage due to the formation of microscopic blood clots in capillaries and small arteries.

Tissue Factor Pathway Inhibitor or TFPI – an anticoagulant protein that inhibits early phases of the procoagulant response.

XTEN technology – a process to slow the breakdown of FVIII.

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