CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

etranacogene dezaparvovec (Hemgenix)

(CSL Behring Canada Inc.)

Indication: For treatment of adults (aged 18 years of age or older) with Hemophilia B (congenital Factor IX deficiency) who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes

October 17, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Input

Name of drug	**etranacogene dezaparvovec**
Indication	**Hemophilia B**
Name of the patient group	**Canadian Hemophilia Society (CHS)**
Author of the submission	**David Page with input and review from members of the CHS Blood Safety and Supply Committee**
Name of the primary contact for this submission	**David Page** **Consultant, CHS**
E-mail	[redacted]
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October 16, 2023

About our patient group

Its mission is to advocate to improve the health and quality of life for all people in Canada living ounded in 1953, the FCanadian Hemophilia Society (CHS) is a national voluntary health charity.
with inherited bleeding disorder until cures are universally available. Its vision is a world free from the pain and suffering of inherited bleeding disorders.

The Canadian Hemophilia Society, whose **national headquarters** are in Montreal, is an organization that works at three levels: nationally, provincially and locally. We have **ten provincial chapters** across the country. Some of our chapters have additional local structures that we refer to as regions.

Its **Board of Directors** is made up of individuals with valuable skills and representing the organization's ten provincial chapters. Each provincial chapter in turn is managed by its own Board of Directors. Many chapters are separately incorporated and have their own charitable registrations. Three provinces—**Québec**, **Ontario** and **Manitoba**—currently have offices with permanent staff. All chapters work in accordance with **CHS by-law** and conform to national policies. The national organization and its ten chapters share a common vision and mission. The CHS has approximately 300 active volunteers across the country.

The CHS is affiliated with the **World Federation of Hemophilia** which is officially recognized by the World Health Organization. We work in collaboration with health care providers in Canada's 26 inherited bleeding disorder **comprehensive care treatment centres**, the blood system operators (Canadian Blood Services and Héma-Québec), the Network of Rare Blood Disorder Organizations, the rare disease community, and others who share our common interests. Charitable Registration: 11883 3094 RR 0001 Website: **www.hemophilia.ca**

Information gathering

The CHS gathers information on the patient perspective in a number of ways.

The CHS Blood Safety and Supply Committee (BSSC) is made up of a dozen patients, physicians and nurses. Meeting monthly, their role is to inform and advise the Board of Directors and the community on key issues pertaining to the safety, efficacy and availability of coagulation therapies for inherited bleeding disorders. Collectively, they have over 200 years of experience in this field. Members of the BSSC attended the latest Congresses of the International Society of Hemostasis and Thrombosis (Montréal, June 24-28, 2023) and the World Federation of Hemophilia (Montréal, May 8-11, 2022), where the latest research on novel therapies was presented.

Gene therapies for hemophilia B have been in clinical trials for more than ten years. The CHS and its BSSC have closely followed the results of this research by attending medical conferences where results are presented, and reading peer-reviewed journal publications. Every two years, the CHS, in collaboration with the Association of Hemophilia Clinic Directors of Canada, organizes a three-day medical/scientific symposium where the latest research is presented and discussed. People with hemophilia B from Canada and abroad who have received gene therapy in clinical trials have presented their experience at these meetings. The latest symposium was held May 4-7, 2023. A session, entitled **GENE THERAPY: MANAGING EXPECTATIONS** was dedicated to gene therapy, including patient perspectives, and can be viewed at … **https://youtu.be/rDumGahug-Y**

“Hemophilia gene therapies: the current state of affairs”
Presented by DR. DAVID LILLICRAP, Kingston General Hospital, Ontario **https://youtu.be/onc1WwlZdmY**

"Why I said 'Yes' to gene therapy"
Presented by LUKE PEMBROKE, Greenwich, England, United Kingdom **https://youtu.be/HJv53a31gXQ**

"Why I said 'No' to gene therapy"
Presented by RICK WAINES, Victoria, British Columbia **https://youtu.be/J1-tpIlqIHI**

“Updates on hemophilia gene therapies clinical trials in Canada”
Presented by DR. ALFONSO IORIO, Hamilton Health Sciences Centre, Ontario **https://youtu.be/CT4VYCGdY5I**

“Hemophilia gene therapies roll-out: are HTCs ready?”
Presented by DR. ROY KHALIFÉ, The Ottawa Hospital, Ontario, and DR. JERRY TEITEL, St. Michael’s Hospital, Toronto, Ontario

https://youtu.be/W5lxTsJ3gjY
Open discussion with panel
Moderator: DR. ROY KHALIFÉ, AHCDC
Panelists: DR. ALFONSO IORIO, DR. DAVID LILLICRAP, DAVID PAGE, LUKE PEMBROKE, MARK SKINNER, DR. JERRY TEITEL, RICK WAINES

The CHS is in regular contact with its members through chapter meetings where current and future therapies of all types are discussed. In addition, members of the BSSC are in regular contact with their counterparts in hemophilia patient organizations around the world and the BSSC is represented on the World Federation of Hemophilia’s Coagulation Products Safety, Supply and Access Committee.

To collect specific perspectives from patients and caregivers with hemophilia B on the burden of disease and treatment, satisfaction with current treatment and the improvements people would like to see in a new treatment, the CHS conducted an online survey in English and French, launched on July 10, 2023 and open until October 12, 2023. The survey was publicized via different CHS and chapter communication tools, including the CHS website, e-mail, Facebook, Twitter and Instagram. The questions asked are identical to those in the CADTH patient input template. We received 49 responses up to October 12 2023. All respondents are affected by severe or moderately severe hemophilia B without inhibitors. Not all respondents answered each question. The results of that survey are presented in SECTIONS 3, 4, and 5.

The Canadian Hemophilia Society participates in the PROBE (Patient Reported Outcomes, Burdens and Experiences) study (https://probestudy.org/). As a result of promotion by the CHS and collaboration with the Canadian Bleeding Disorder Registry, Canada has the highest proportion of patients competing the survey among more than 50 participating countries. The PROBE study collects data not only from people with hemophilia but also from those without hemophilia. Patient reported outcomes in Canadians with severe hemophilia B compared with controls are presented in SECTION 3.

In addition, in September 2022, the CHS conducted an online survey of Canadians with severe hemophilia A and B to learn their hopes and expectations for gene therapy and received 39 responses. The results of that study are presented in SECTION 5.

Disease experience

Joint damage, primarily to knees, ankles and elbows, caused by repeated internal hemarthroses, is the primary physical health impact of hemophilia B. Bleeding can be caused by very minor trauma. These impacts are clearly reflected in the survey results.

Overall quality of life

- *Reduction in quality of life. Constant worry about injuries and bleeding, and the long recovery time. Twice-weekly treatments.*
- *The exclusion from certain activities is a real factor in mental health. As an adult, not being able to participate in household duties, the chronic pain, knowing that I will have even more limitations in the future, not being able to contribute to savings for later invalidity, the worry that I will be a burden on loved ones; all these weigh on me.*
- *For the most part I manage well. Other than the arthritis that comes from damaged joints, I can function somewhat normally.*

The need to refrain from physical activities and sports

- *As an adult, hemophilia has a big impact on my daily life. Many activities are chosen relative to my condition. I try to limit the risk of injuries. Even my career choice was affected by hemophilia.*
- *My son has severe hemophilia B. There are certain activities he has to be careful doing or can't do at all. A small injury can easily become a trip to the hospital and weeks of recovery.*
- *I take caution re activities, even benign sports.*
- *There is constant worry that when a trauma happens there will be a delay in treatment and life-threatening response times.*
- *We must make careful decisions about activities that come into play now that he is older.*

Reduced mobility

- *My mobility, strength and endurance are significantly impacted on a daily basis.*
- *I have joint pain and stiffness in knees and ankle that make walking painful and joint pain and stiffness in elbows that limit certain functions.*
- *He is now too heavy for us to carry if he has a bleed that affects his walking. We have a wheelchair for him for these instances.*
- *My joints are affected. Lots of pain, every day. I've had lots of surgeries and can't function normally.*

Joint replacements

- *I have had several joint replacements and severe back pain due to the hemophilia.*
- *I have had two knee replacements in the last five years.*

Patient reported outcomes from PROBE study

These data, valid as of October 12, 2023, include 134 reports from male Canadians, aged 18 and up, with severe hemophilia B; and 132 male Canadian controls, aged 18 and up, without a bleeding disorder, collected through the PROBE study (**https://probestudy.org**).

Outcomes reported	134 male Canadians, aged 18 and up, with severe hemophilia B	132 male Canadian controls, aged 18 and up, without a bleeding disorder
On regular prophylaxis	91%	NA
On intermittent prophylaxis	5%	NA
On on-demand treatment	3%	NA
Limited range of motion in one or more joints	91%	NA
Used mobility aids in last 12 months	37%	6%
Used pain medication in last 12 months	81%	43%
Experienced acute pain in last 12 months	57%	30%
Experienced chronic pain in last 12 months	78%	32%
Have difficulties with activities of daily living	54%	11%
Have moderate or severe difficulties walking	47%	3%
Work full-time or part-time	65%	70%
Retired due to health	23%	0%
Unemployed due to health	20%	0%
Made education/career decision due to health	28%	18%
Days missed from school/work in last 12 months	21	10
PROBE score	0.709	0.902

Experiences with currently available treatments

The only currently approved products for the treatment of hemophilia B are clotting factor concentrates containing factor IX. Treatment for severe and moderately severe phenotypes of hemophilia B is for the vast majority of patients by regular prophylactic (preventative) intravenous infusions (IV), usually administered at home. Both recombinant and plasma-derived formulations are available in Canada. Recombinant forms can be either “standard half-life” preparations which require two to three IV infusions per week or “extended half-life” preparations, usually requiring only one infusion per week.

These treatments are prescribed through the Canadian network of 26 hemophilia treatment centres and are available at no direct cost to the patient through the Canadian Blood Services Plasma Protein and Alternative Products Formulary or

Héma-Québec. Typically, patients/caregivers go to the treatment centre or hospital blood bank every one or two months to replenish their home inventory. In addition, they have more in-depth assessments by the interdisciplinary care team once or twice per year.

No alternatives to IV factor IX are currently approved. This is unlike hemophilia A where monoclonal antibodies (emicizumab) mimicking the function of factor VIII and injected subcutaneously are in widespread use. Subcutaneous non-factor IX replacement therapies to treat hemophilia B are in clinical trials. These include anti-tissue factor pathway inhibitors such as concizumab (licensed in Canada for those with inhibitors to factor IX) and marstacimab, anti-antithrombin therapies such as fitusiran, and anti-protein C therapies. It is difficult to predict if and when these products will get marketing approvals in Canada. See **www.hemophilia.ca/products-in-the-pipeline**.

Early initiation of prophylaxis provides continued protection against joint damage throughout childhood compared with delayed initiation, but early prophylaxis is not sufficient to fully prevent damage. At the exit of the landmark Joint Outcome Continuation Study in hemophilia A, MRI osteochondral damage was found in 77% of those on secondary prophylaxis and 35% of those on primary prophylaxis. (Beth Boulden Warren, Marilyn J. Manco-Johnson et al. **https://doi.org/10.1182/bloodadvances.2019001311**, Blood Adv (2020) 4 (11): 2451–2459.)

While joint health research on hemophilia B lags behind that of hemophilia A because of the smaller numbers affected, there is little reason to believe that results are different. As long as factor levels fall below 10-15%, as is inevitable with factor replacement therapy, joint damage will occur in the long term. Only maintenance of higher levels will avoid this. **I. E. M. Den UIJL**, **E. P. MAUSER BUNSCHOTEN**, **G. ROOSENDAAL**, **R. E. G. SCHUTGENS**, **D. H. BIESMA**, **D. E. GROBBEE**, **K. FISCHER https://doi.org/10.1111/j.1365-2516.2011.02539.x**

This is how 27 respondents to the recent survey rated their satisfaction with current treatments.

- Very satisfied 5 (19%)
- Satisfied 14 (52%)
- Neither satisfied nor dissatisfied 7 (26%)
- Dissatisfied 0 (0%)
- Very dissatisfied 1 (4%)

Patients and caregivers described their current treatments.

Safety and efficacy

- *Current factor concentrates protect well against most bleeding. I have approximately 2 to 3 joint bleeds per year despite prophylaxis.*
- *While receiving his factor, my son is can run around like a normal kid, with minimal bleeds.*
- *The support and care we get at the_____ Children's Hospital are excellent. They are very knowledgeable and willing to help. I just wish my son didn't need to have so many needles all the time.*
- *Bleeds seem to be controlled. We are very careful so this could be because of our efforts.*
- *The concentrates are reasonably effective in protecting against bleeding.*
- *With the EHL products, he doesn't bruise as easily now and has 1 or 2 minor bleeds per year, commonly in his ankle. No side effects or inhibitors.*
- *Our current long-acting clotting factor works great. It is easy to use and infuse; however, so many pokes (IV infusions) every single year can be traumatic.*
- *The current treatment regime had to be adjusted to be given within a shorter time line as additional bleeds were happening.*
- *We recently changed from an SHL product to an EHL. The number of treatments went from three times a week to one. That is a huge plus. Both medications have worked well.*
- *We use an EHL FIX once a week through IV infusion. This is usually enough factor for him to get through a 7-day period without any bleeds. On this prophylaxis schedule, generally in one year we may need to take him to the Children's Hospital 1-2 times per year to treat a bleed.*
- *He has missed some school with bleeds to improve healing.*

- *The factor IX only lasts 24 hours in the bloodstream so if you have a major trauma it means several days of infusions.*
- *The longer acting treatment is not working in the timeline expected.*

The burden of treatments

- *The treatments, even if they're just IV infusions, greatly complicate everyday life, travel, and leisure activities.*
- *I don't do well dealing with treatments as I am prone to forget.*
- *Infusions can be difficult because the success of the needle getting in the vein is dependent on his vein visibility at the time of injection. A side effect would be that over the years he has complained about pain at the injection sites of his hands.*
- *It is super hard and I have always been hard to infuse.*
- *Injection sites are scarred.*
- *An IV infusion every 5 days. I manage despite poor veins.*
- *He has to have needles for factor replacement every week, and blood tests way more often than any other kid. A small injury can easily become a trip to the hospital and weeks of recovery. Then he gets more needles to add more factor IX to his blood to try to speed up his recovery.*
- *Regular treatments are only a slight nuisance.*
- *I get frequent phone calls from school due to cautious staff members not familiar with this disorder.*
- *I give him weekly infusions, or more if injured, through a port.*
- *The side effects are with my veins. I feel them getting used up. They are more and more discoloured. The aesthetic aspect bothers me.*
- *Thankful that my son has had access to treatment without the same risks as 30 + years ago. However, I know he would be even more satisfied if he could get a possible longer term treatment, such as gene therapy.*

Socioeconomic aspects

- *There are a fair amount of trips to the clinic, so time off work for parents.*
- *The clinic visits and follow-up are seemingly more difficult to access and professional staff positions are not always filled.*
- *The difficulties in accessing treatment are mostly time off work if something happens and we need to take him to the hospital. We live fairly close to the _____ Children's Hospital. One of the reasons we live where we do is because of the access to the hospital.*
- *Travel and insurance are an issue.*
- *I take time off work to take my son to appointments. He needs frequent blood tests. He has pain at injection sites. Going to ER when clinic is closed is often a bad experience. Parking costs at hospitals are super high.*
- *I have 6-8 clinic visits per year to pick up concentrates and have blood tests. I have to miss work.*

Improved outcomes

In September 2022, the CHS conducted an online survey of Canadians with severe hemophilia A and B to learn their hopes and expectations for gene therapy and received 39 responses. The survey, whose answers were anonymous, was targeted at Canadian residents with severe hemophilia A or B, fourteen years of age or older, who represent the patient group that might consider taking gene therapy in the next five years.

The survey was publicized via the usual via CHS communication channels: website, Facebook, Twitter, and certain chapters' social media, and was available in both English and French.

Thirty-nine people completed the survey, 31 with hemophilia A, seven with hemophilia B and one not specified. This accurately reflects the prevalence of severe hemophilia A and B in the population.

Fifty-four percent (54%) indicated they thought they would be eligible for gene therapy, 28% thought they would not be eligible and 18% said they didn't know. Reasons for thinking themselves to be ineligible include a past history of inhibitors, pre-existing antibodies to the AAV vector used to deliver the gene for factor VIII or IX, age (under 18 or over 75) and other medical conditions, for example, active liver disease.

Respondents were asked the minimum level of factor VIII or IX expression predicted to be achieved that would make them want to have gene therapy. Answers varied widely, but 60% hoped for sustained expression of 30% or more.

Table 1: Minimum factor VIII or IX expression desired

Minimum factor VIII or IX level desired (normal is 50-150%)	% of respondents
5-10%	7%
10-20%	17%
20-30%	7%
30-40%	17%
40-100%	43%
I don't know	10%

Respondents were also asked how long they would expect the factor level they chose in the question above to last for them to accept gene therapy. Again, answers varied widely, which is not surprising given that clinical trials for hemophilia gene therapy have given no clear answer to this question. It is worth noting that more than 6 out of 10 respondents (63%) indicated they expected gene therapy to be effective in preventing bleeding for at least 10 years. **Table 2: How long desired factor level should last to be acceptable**

Time that gene therapy will be effective	% of respondents
My whole life	40%
More than 10 years	23%
5-10 years	10%
3-5 years	3%
Time that gene therapy will be effective	**% of respondents**
Less than 3 years	7%
I don't know	17%

Respondents were asked how much certainty they needed as to the factor VIII or IX level they might achieve. More than half (56%) need to be *quite sure* or *absolutely sure* of the eventual factor level obtained. Unfortunately, clinical trial results, especially in hemophilia A, show a highly variable and unpredictable level of response from individual to individual, ranging from no response at all to levels above normal.

Table 3: Level of certainty needed regarding level and duration of factor expression

I need to be absolutely sure of the factor VIII or IX level I will get.	13%

I need to be quite sure of the factor VIII or IX level I will get.	43%
I am ready to accept some uncertainty.	20%
I realize my factor VIII or IX level could be much lower or higher than expected and I am ready to take a chance.	17%
I don't know.	7%

Respondents were asked if they would accept gene therapy if they were told in advance that steroids would probably be needed in the period following administration. Thirty-eight percent (38%) said yes, 21% said no and 41% didn't know. Many respondents commented that this was an important factor that would cause them to pause. Many others indicated they needed more information on this subject.

The survey asked if people would accept to receive gene therapy knowing that that there would be frequent blood draws in the weeks and months following administration, and they would need to be followed up in a registry for 10 to 20 years. Sixty-six percent (66%) answered yes, 10% answered no and 24% didn't know.

Respondents were asked to express their overall attitude to gene therapy. (More than one answer was allowed.)

Table 4: Overall attitudes to gene therapy

I am very interested in receiving gene therapy.	45%
I am not interested in receiving gene therapy at this time.	14%
I am concerned about short-term side effects.	35%
I am concerned about long-term side effects.	52%
I am concerned that FVIII or IX levels will not be high enough to prevent bleeding.	44%
I am concerned that FVIII or IX levels will not last long enough.	55%
I am waiting for more information.	48%
I intend to wait for future generations of gene therapy.	31%
I am ready to take a chance.	10%
I am not ready to take a chance.	28%

We asked respondents to indicate how knowledgeable they felt themselves to be.

Table 5: Level of knowledge about gene therapy

Very knowledgeable	13%
Quite knowledgeable	16%
Somewhat knowledgeable	38%
Not very knowledgeable	29%
Not knowledgeable at all	3%

Respondents also indicated what they would like to know more about. Answers were:

- *Everything.*

- *Nothing. I just wouldn't do it.*
- *Nothing, I trust the science. I just want it.*
- *How the therapy can be improved to provide better and more consistent results.*
- *How to avoid the exclusion of those with HIV and/or HCV infection.*
- *The complete working of it.*
- *The experiences of those who have gone through the process.*
- *Why and how it lasts for the amount of time that it does.*
- *More about side effects.*
- *If additional doses are possible if my levels drop, especially with future generations of gene therapy.*
- *How it's being developed safely and securely.*
- *Side effects, long term effectiveness.*
- *Parallel information from other gene therapies for other disorders.*
- *Trough levels, duration of levels, risks.*
- *Cognitive/neurological risks.*
- *Risks of comorbidities.*
- *Will government be inclined to pay for gene therapy?*
- *The kinds of support that would be available to a person in the first few weeks and months when there are numerous blood draws and appointments with medical personnel.*
- *The lasting effects for those who went through clinical trials and received corticosteroids.*
- *If I don't respond, can I go back to my previous treatment with factor?*
- *The long-term risks.*

Patients and caregivers with hemophilia B, via the July 2023 survey undertaken for the review of fidanacogene elaparvovec, told us this about how gene therapy could potentially change their lives.

- *How can it not? Nothing beats even a year of no infusions or bleeds.*
- *Gene therapy would totally change my life. It would free me from regular injections. Even if I had to take the occasional one, I wouldn't have to struggle so hard to administer the product and find a vein. I wouldn't have to pick up factor as often and save needless trips to hospital. My joints would be healthier from fewer bleeds and I could walk and carry things easier. I'd have less pain. Mentally, I'd be less anxious, less stressed, more relieved and relaxed. My quality of life would increase and I could be free to travel more, to be more physically active and to focus on other priorities without the issue of bleeds hanging over my head. A weight lifted off.*
- *I think that this treatment will not only make an impact on my life but on many others with this disorder. Our whole lives we have had to be worried about keeping up with our medication and doing low risk activities, and being told no you can't do something because it's too dangerous for you while we watch other people our age go do the same activity. I know when I was a child I found that very difficult because there were so many things i wanted to do that I never could. This treatment is something I thought only was possible in my dreams. My mental and physical health would get a huge boost from this as I would be in an easier state of mind not having to constantly remember to do factor every week and make sure my levels are high enough to do activities.*
- *I feel gene therapy, if proven safe through trials, would have a huge impact. Being able to engage in sports without the worry and stress that comes from having hemophilia would be a big stress reducer. Mentally, it would be very impactful. Even though you come to terms with it, it still always ligers in your mind. My son has always looked forward to the day that there may be a cure. I think it would have a huge positive impact on his mental health as well as the obvious physical benefits.*
- *Gene therapy would transform my life. I wouldn't bleed. People who don't have hemophilia cannot imagine the pain of a joint bleed; they have no idea.*
- *I could imagine it being quite fantastic. Minimal needles, less stress and hopefully even fewer bleeds.*
- *Gene therapy could revolutionize my daily functioning. It could optimize my current health state and improve my quality of life by reducing the amount of time and energy expended on treatments and preventing bleeding episodes.*

- *Gene therapy would be life-changing for my son. He would go from having 52-75 needle pokes per year to only needing 2-5 needles with gene therapy. If his factor IX levels are consistently high from gene therapy, he can participate in activities that his doctors told us he can't because of physical contact. He tells me he always has to be aware of what dangers there are, even if they are minor. Something as minor as a hit with a ball or a bump against the wall can cause a bleed. Gene therapy could take some of his worries away if he doesn't have as high of a chance of a bleed. He wouldn't have bruises all over his body all the time. We would also have less trips to the hospital.*
- *Confidence to travel and do physical work.*
- *Less restrictions on activities. No weekly prophylaxis. No medications needed. A sense of safety knowing he has factors at all times in his body.*
- *No more traumatic needles weekly. No more worry of injury response time. Ability to go out and take trips longer than a week without worry.*
- *Gene therapy is a game changer. Going into teenage/adulthood, gene therapy would be huge for mental health and him feeling more "normal" and being able to enjoy life more fully.*
- *Gene therapy has the potential to keep my factor IX at a level that would be very effective in preventing bleeding (i.e. 30-40%). I would no longer need IV infusions, except for surgeries or serious trauma.*
- *Gene therapy would help my son dramatically without the fear of constant injuries. Mentally, removing his phobia around needles would improve his lifestyle incredibly.*
- *I could travel more easily. Now, I limit my travel because of the difficulty of carrying bulky medication. Without 2 to 3 infusions per week, I'd have more time for my family and to do activities that improve my quality of life.*
- *It would make the last years of my life so much easier.*

Experience with drug under review

A small number (likely close to five) Canadians have undergone gene therapy for hemophilia B, but nothing is known to the CHS about their experience outside the preliminary data for the full trials.

In early 2023, with the approach of gene therapies to the Canadian market, the Canadian Hemophilia Society produced *All About Hemophilia Gene Therapy, A guide for patients and caregivers* (**bit.ly/AllAboutHemophiliaGeneTherapy**).

This is an excerpt from the introduction to the booklet.

> *The hemophilia community has been waiting for gene therapy for years. Many have hoped it would be a cure. 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 onetime 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.*
>
> *People with hemophilia (PwH) and their families must have all the information they need to make a fully informed decision as to whether or not to consider gene therapy.*
>
> *PwH benefit from a number of therapeutic options, many of which have a long track record of safety and efficacy. Therefore, the benefits and risks of gene therapy must be seen in comparison to current treatments.*
>
> *Ten key considerations that will be explored in this booklet include:*
>
> 1. *Gene therapy is not for everyone.*

2. *Many people are not eligible.*
3. *Predicting the outcome of gene therapy for an individual is not possible; however, for some, it can result in a significant improvement in quality of life.*
4. *Gene therapies for hemophilia A and B are different.*
5. *Decisions on moving ahead with gene therapy should be made only after a rigorous process of informed, shared decision-making.*
6. *Recipients of gene therapy must be ready for frequent blood draws and hospital visits in the first months after administration.*
7. *Most of those with hemophilia A and some with hemophilia B will require treatment with corticosteroids for up to many months after administration of gene therapy. These drugs can have significant side effects.*
8. *Reduction in consumption of alcohol may be recommended after gene therapy.*
9. *Clinicians monitoring people after gene therapy must be supported by a network of experienced experts.*
10. *All recipients of gene therapy must be enrolled in a registry. This registry will follow people for life.*

Companion diagnostic test

Testing for antibodies to the AAV vector should be required before undergoing gene therapy. With regard to **etranacogene dezaparvovec**, those who test positive and whose AAV-5 antibody levels are very high may be deemed ineligible. (The antibody level above which gene therapy with **etranacogene dezaparvovec** will be ineffective remains to be determined.) Those who undergo gene therapy are required to have liver enzyme testing one to two times a week in the weeks and months following administration. A process needs to be in place to do the blood draws and send them to a laboratory for immediate analysis. Results must be analyzed very rapidly. Experts in hemophilia gene therapy must be available to advise physicians who are less experienced on when to initiate steroid treatment. Time is of the essence. If a rise in ALTs indicates a possible rejection of the vector, a course of steroids is started immediately and lasts for several months. A failure to act quickly can mean that expression of factor IX is permanently diminished or entirely eliminated. Side effects of the steroids, affecting both physical and mental health, can be significant. Patients and their families need to be adequately counselled regarding the potential need for steroids and their health impacts well in advance of any decision to receive gene therapy.

8. Anything else?

The Canadian Hemophilia Society considers these to be the key results and conclusions from the clinical trial (HOPE-B) with etranacogene dezaparvovec.

1. The phase 3 study showed clear superiority over FIX prophylaxis in preventing bleeding.
2. The mean FIX activity levels were 36.7% 24 months after administration. This is a level that cannot be maintained with FIX prophylaxis and which offers very high protection against bleeding, except in cases of severe trauma or major surgery.
3. Fifty-two of fifty-four patients remained off FIX prophylaxis 24 months after administration. This is evidence of an excellent response in a large majority of people (96%).

4. Ten-year results with an earlier version of uniQURE's gene therapy (same delivery vector but without the Padua gene enhancement) show stable FIX activity. This is evidence of a prolonged response likely exceeding 10 years. This means that etranacogene dezaparvovec can be costeffective in the long term in comparison with FIX prophylaxis, even when taking into account nothing but drug costs.
5. The Phase 3 trial showed no difference in factor IX expression in those with AAV5 antibody scores of 700 or lower; this means a greater proportion of people will be eligible.
6. No treatment-related serious adverse events occurred.
7. The patients' perspectives highlight the clear improvements in health and quality of life that can be expected from this therapy.

APPENDIX: Patient group conflict of interest declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. **Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.**

   The CHS received no help from outside our patient group to complete the submission.

2. **Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.**

   The CHS received no help from outside our patient group to collect or analyze data used in this submission.

3. **List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.**

Table 1: Financial Disclosures

COMPANY	*Check appropriate dollar range*			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer				X
BioMarin		X		
CSL Behring				X
Novo Nordisk				X
Pfizer				X
Roche				X

Sanofi				X
Takeda				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: **Sarah Ford**
Position: **Chief Executive Officer**
Patient group: **Canadian Hemophilia Society**
Date: **October 16, 2023**

Clinician Input

CADTH Project Number: SG0805
Generic Drug Name (Brand Name): etranacogene dezaparvovec (Hemgenix)
Indication: For the treatment of adults with hemophilia B with a pre-existing neutralizing AAV5 antibody titer below 1:900 who currently use FIX prophylaxis therapy, or have current or historic life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

Name of Clinician Group: The Association of Hemophilia Clinic Directors of Canada (AHCDC)
Author of Submission: The Novel Therapy Committee members, on behalf of AHCDC

1. About Your Clinician Group

The Association of Hemophilia Clinic Directors of Canada (AHCDC) is a non-profit organization of Hemophilia Clinic Directors from across Canada. The goal of the AHCDC is to ensure excellent care for persons with bleeding disorders in Canada through clinical services, research and education. Our members are involved nationally and internationally in regulatory trials and research studies that investigate new factor replacement products or regimens, inhibitor development, prophylaxis, quality of life, women with bleeding disorders, genetic and clinical aspects of von Willebrand's disease. In addition, our organization promotes clinical care through support of the National Inherited Bleeding Disorder Genotyping Lab. The AHCDC has been active since 1994. It is currently formed by 26 hemophilia treatment centers (HTC) and has 71 full members. The AHCDC members care for the totality of Canadian patients with hemophilia. AHCDC owns and manages the Canadian Bleeding Disorders Registry (CBDR, formerly CHARMS), a registry platform collecting demographics, clinical and quality of life data of all Canadian patients with hemophilia.

The organization's website is: www.ahcdc.ca

2. Information Gathering

The information is gathered through a scoping literature review, expert presentations and member discussions through the AHCDC National Gene Therapy Learning Initiative (November 11, 2022), and drafted by members from the AHCDC Novel Therapy committee. It is circulated to AHCDC members for input and feedback before submitting the final version.

3. Current Treatments and Treatment Goals

Hemophilia B is an X-linked recessive bleeding disorder, affecting approximately 1 in 50,000 people, or about 600 Canadians [1]. The 2020 Canadian Hemophilia Registry reported a total of 526 adult males (³18 years) registered in one of the 26 Canadian hemophilia treatment centres (HTCs), of whom 352 has moderate or severe hemophilia B [2]. Hemophilia B is classified as mild (baseline factor IX [FIX] activity 0.05-0.40 IU/ml), moderate (FIX 0.01-<0.05 IU/ml) and severe (FIX <0.01 IU/ml). Persons with severe hemophilia B and a proportion of moderate hemophilia B present with a clinically "severe" bleeding phenotype [3]. They suffer from recurrent bleeds into joints and muscles (spontaneous and traumatic), which may be mitigated but not eliminated by

prophylactic treatment. Repeated bleeds into joints result in progressive joint damage (hemophilic arthropathy), chronic pain, loss of function, impairment in school and work productivity, and the need for early orthopedic interventions such as joint arthroplasties.

The current SOC in Canada adheres to the World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia. Persons with hemophilia (PWH) with a non-severe bleeding phenotype typically treat with episodic (also known as on-demand) clotting factor concentrates (CFCs) at the time of joint and muscle bleeds, and treat with tranexamic acid for mucocutaneous bleeding. For PWH with a severe bleeding phenotype, the WFH strongly recommends prophylactic replacement with CFCs or non-factor replacement therapy [3]. The goal of prophylaxis, the regular administration of therapeutic agents aimed at maintaining hemostasis, has evolved over the past decade. Historically, the primary goals of prophylaxis were to prevent repeated bleeding into joints and muscles which was supposedly achievable by maintaining FIX trough >0.01 IU/ml at all times, also preventing life-threatening bleeds such as intracranial hemorrhage, and prevent/slow down joint damage. Over time it became clear that prophylaxis targeting the 0.01 IU/ml threshold was only partially effective, and more so when associated with a careful avoidance of any moderate to intense physical activity, including the practice of most sports. Due to the very large variability in response to the infusion of CFCs, the administration of standardized doses of CFCs was producing higher trough levels in a sizeable minority of patients, showing the benefits of targeting higher trough level, which would have been achievable for many patients only with impractical very frequent administration of very high dose of concentrates. Later on, higher trough levels became achievable for a larger majority of patient with the availability of extended half-life factor concentrates. More recently, the updated WFH Guidelines emphasized other important goals to aim for minimal bleeds and **to empower PWH to lead healthy and active lives, and to participate fully in physical and social activities similar to the general population** [3]. For PWH with breakthrough bleeds despite routine prophylaxis, the WFH recommends individualization and escalation of prophylaxis dose and/or frequency to prevent bleeding at all times. The current SOC in Canada includes individualized or personalized prophylaxis, based on patient- and disease-related factors such as bleeding rates, joint health, physical activity and occupation, population pharmacokinetics profile on CFCs, and need for antiplatelet or anticoagulant therapy. Currently, approximately 80% of Canadian patients with clinically severe hemophilia B are receiving prophylaxis.

In Canada, CFCs are provided by the Canadian Blood Services (for provinces outside of Quebec) and Hema-Quebec (in the province of Quebec). Currently available products include standard half-life factor CFCs (Benefix®, Rixubis®) and extended half-life CFCs (Alprolix ®, Rebinyn®). Non-factor replacement therapies are currently available only through clinical trials, although may eventually become available in the Canadian market within the next 2-5 years. These include RNA interference therapy targeting antithrombin (fitusiran), and monoclonal antibodies against tissue factor pathway inhibitors (anti-TFPI). One of the anti-TFPIs, concizumab, is recently licensed in Canada but only for hemophilia B with Factor IX inhibitors. Current treatments for hemophilia only target symptoms (prevention of bleeds or joint damage), without the ability to modify underlying disease mechanism, natural history, or provide potential cure. Prophylactic CFC replacement requires frequent intravenous (IV) infusions long-term, typically 1-2 times per week. The frequency of infusions, the consequences of breakthrough bleeds, and the need for IV access pose significant disease and treatment burden for patients, families, and caregivers. The latter barrier is particularly applicable to infants, children, and some older adults.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There are several unmet needs despite the currently available treatments in Canada for PWH with severe bleeding phenotype. First, prophylactic CFC replacement requires frequent venipuncture by patients and/or caregivers long-term, typically 1-2 intravenous infusions per week. Even with the advent of population pharmacokinetics and extended half-life FIX products, less than half of PWH are able to administer less than once weekly (e.g. every 10-14 days). Many individuals have poor venous access, posing a major challenge to routine prophylaxis. While placement of a central venous catheter (generally a Port-a-catheter) is an option, it is associated with long-term complications including risks of infection, bleeding, thromboembolism, and loss of function requiring removal. Even among PWH with adequate venous access, non-adherence and/or treatment burden pose as key barriers to effective prophylaxis. For persons with hemophilia B and a severe bleeding phenotype, **there is an unmet need to restore coagulation factor to clinically effective levels without the need for frequent venipunctures on a regular basis throughout one's lifespan.**

Second, **the efficacy of prophylaxis with CFCs is variable across individuals**. Given the half-life of CFCs, even with frequent administration of routine prophylaxis 1-2 times per week, PWH may experience low FIX trough levels (e.g. 0.01-0.05 IU/ml) prior to the next infusion. As a result, they are susceptible to breakthrough bleeds into joints and muscles, resulting in pain, loss of function, absenteeism from work or school, and more importantly progressive joint damage. Even with the routine adoption of individualized, pharmacokinetics-guided prophylaxis (adjusting dose and/or frequency) in Canada, many PWH are still unable to achieve the goal of zero bleeds. For the period from January-December 2021, data from 149 severe hemophilia B patients on regular prophylaxis in Canada were available: of these patients, 55/149 (37%) had at least one hemarthroses in the calendar year. Additionally, 15 patients (10%) had a major bleeding episode.

Third, current treatments do not modify or alter the course of disease. Awareness of the progressive decline of trough factor IX levels following each factor concentrate infusion, many PWH live a restricted life, modifying their physical and social activities due to fear of bleeding and treatment burden. The impact on quality of life and participation varies among individuals, and may include (but not limited to): inability to pursue certain occupations, inability to participate in certain sports or physical activities, fear of bleeding or pain with sexual activities, mental health problems related to treatment burden, and chronic pain. The impact of hemophilia on quality of life has been highlighted in a number of studies [4-7].

Fourth, the factor IX trough levels associated with prophylaxis regimens are often insufficient to allow for safe anticoagulation or dual antiplatelet therapy. Historically, PWH have a shorter life expectancy than the general population due to life-threatening hemorrhages, as well as blood-borne pathogens such as human immunodeficiency virus (HIV) and hepatitis C from tainted blood products. As the life expectancy of PWH is approaching that of the general population, we observe a rise in the prevalence of cardiovascular and cerebrovascular diseases requiring antiplatelet or anticoagulation therapy. This provides a clinical conundrum, and is challenging to manage even with the use of aggressive prophylactic therapy.

Overall, there is a pressing need to provide effective therapy for a subgroup of PWH with a severe bleeding phenotype, who continue to experience breakthrough bleeds into joints/muscles despite routine prophylaxis. The ultimate goal, in keeping with the WFH treatment guidelines, is to minimize the number of bleeds to zero or near-zero, slow down the progression of hemophilic arthropathy, and minimize the adverse impact of recurrent bleeds on physical activity, physical and social function, and productivity loss. Among PWH with currently low rates of bleeding on prophylactic therapy, there is an unmet need to provide a therapy with curative potential, that would provide clinically adequate factor levels without long-term need for prophylactic replacement. This would improve health-related quality of life, reduce treatment burden, and save costs in the intermediate to long-term.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

As currently available hemophilia therapies (factor or non-factor replacement therapy) do not provide a curative option, gene therapy complements other available therapies by providing the possibility of long-term phenotypic cure for persons with hemophilia B. Hemophilia B is an X-linked monogenic disease leading to a single plasma protein deficiency. This pathology, along with the wide therapeutic margin of factor VIII and FIX levels have made hemophilia A and B recognized as ideal candidates for gene therapy for decades. Gene therapy provides a one-time treatment that inserts a functional factor IX gene into somatic cells, leading to sustained factor IX production. For the first time, we now have a treatment option that addresses the underlying disease process and natural history, rather than symptomatic management, representing a paradigm shift.

Until gene therapy can provide widely available, reliable long-term phenotypic normalization, prophylaxis with CFCs will remain the first-line treatment for PWH with a severe bleeding phenotype. Gene therapy is not currently studied in the pediatric population. For adults with hemophilia who continue to experience breakthrough bleeds despite routine prophylaxis with CFCs or non-factor replacement (if available), who are unable to tolerate or adhere to prophylaxis, or who experience impaired health-related quality of life, impaired physical or social function related to hemophilia, gene therapy will be a very attractive therapeutic option.

In contrast to patients with hemophilia A, who have the option of emicizumab (a bi-specific monoclonal antibody mimicking the function of factor VIII, injected subcutaneously), patients with hemophilia B have no current alternatives to CFCs outside of clinical trials. This makes the need for gene therapy all the more pressing in hemophilia B.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Suitability and patient selection have been published in international guidelines and expert opinion pieces. A thorough assessment of eligibility is required, and will be conducted by one or more specialists in hemophilia care (i.e. HTC Clinic Directors). Mechanisms will be in place to ensure equitable access to all eligible patients. Shared decision-making is a key aspect of the patient selection process, ensuring an individualized treatment decision based on clinical and treatment factors, as well as patient's values and preferences. This is especially relevant to gene therapy, as it is a one-time treatment at the present time without options for re-treatment. Patient identification includes:

- Clinical examination and clinical judgment: annualized bleeding rate (all bleeds and bleeds into the index joints which include ankles, knees and elbows), annualized spontaneous bleeding rate (all bleeds and bleeds into the index joints), annualized utilization of factor or non-factor replacement therapy (factor IX, or non-factor replacement therapies accessed through clinical trial), annualized number of factor IX infusions, adherence to prescribed prophylactic infusions, venous access, index joint scores using a standardized index joint examination such as the Hemophilia Joint Health Score (HJHS) performed by an experienced health care professionally (generally a certified physical therapist), and validated outcome measures of health-related quality of life (HRQoL), treatment burden, chronic pain and disability, and ability to adhere to post-treatment laboratory tests

- Laboratory tests: complete blood count and differential, liver enzymes, liver synthetic function, renal function, coagulation factor IX activity, factor IX inhibitor, assessment for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C (serology and/or viral load, if relevant)

- Imaging studies (if needed): abdominal ultrasound, +/- abdominal/liver ultrasound with elastography (i.e. Fibroscan)

- Companion diagnostic tests: neutralizing antibody assay to identify pre-existing antibodies against AAV-5 vectors. As only patients with a pre-existing neutralizing AAV-5 antibody titre below 1:900 are deemed eligible, this will be a first step in eligibility assessment. The AHCDC does not foresee any barriers or concerns with the adoption of centralized testing for AAV-5 antibodies.

Eligible candidates include those with clinically severe bleeding phenotype requiring prophylaxis, no history of inhibitory antibodies, no significant comorbidities, and anti-AAV neutralizing antibody titre <1:900. PWH who are not currently receiving prophylactic therapy (e.g. due to poor venous access, or adherence issues with routine prophylaxis), but who experience repeated, serious spontaneous bleeding episodes, or have a history of life-threatening hemorrhage, are also candidates for gene therapy. For candidates with potential concerns on liver function (based on clinical history and laboratory evaluation), dedicated liver imaging with elastography and hepatology consultation are required. Given the possibility of corticosteroids use for adverse events, candidates should ideally have no absolute contraindications to corticosteroids such as severe psychiatric conditions, poorly controlled hypertension or diabetes, and severe osteoporosis. There are no concerns on misdiagnosis, under- or over-diagnosis in clinical practice.

At this time, it is unclear what are clinical or laboratory predictors of treatment response. This is an important area under study. However, the following factors will be considered to prioritize which candidates may benefit the most from gene therapy: severe bleeding phenotype (regardless of baseline factor IX activity) despite regular prophylaxis; poor venous access; non-adherence to routine prophylaxis resulting in recurrent bleeds; significant impairment in health-related quality of life and/or treatment burden from prophylaxis; need for a higher sustained FIX level (e.g. need for anticoagulants or dual antiplatelet therapy), ability to attend regular clinic follow-up and laboratory monitoring; and ability to abstain from alcohol for 6 months or longer post-infusion.

Given the need for anti-AAV antibody assay, detailed liver assessment, and assessment of PWH attitudes and perceptions, it is difficult to estimate the proportion of PWH eligible for gene therapy once it becomes commercially available. A recent single-centre study in Europe showed that most severe hemophilia A and B patients could not be enrolled due to eligibility criteria or lack of patient interest, only 8% of the patient population were eligible for a gene therapy trial [8].

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

A core outcome set for evaluating the efficacy, safety and value of gene therapy, incorporating both clinical outcomes and patient-reported outcomes, has been developed and proposed [9]. The core outcomes were selected based on a rigorous process including literature review, stakeholder engagement (PWH, clinicians, researchers, regulators and payers, including Health Canada) and adopting a Delphi methodology. The steering group included an AHCDC member. The core set has been endorsed by the World Federation of Hemophilia (WFH) gene therapy working group, and included in the data collected by the Gene Therapy Registry. Its use has been endorsed as post-marketing surveillance system by all drug manufacturers, FDA and EMA (the latter official statement still pending after completed review). Of note, the CBDR has been recently updated by releasing a gene therapy module, colleting all the information included in the WFH Gene Therapy Registry. Canadian centers are ready to collect a thorough set of efficacy and safety outcomes.

The list of key outcome measures established by the WFH working group include:

Clinical outcomes

- Annualized frequency of bleeds (including spontaneous vs traumatic bleeds, treated vs non-treated bleeds): This is routinely collected by patients/ families on the MyCBDR platform, and reviewed annually or more frequently by the HTC team.
- Factor activity level: This will be regularly measured in a central coagulation laboratory. The frequency of Factor IX levels (one-stage, chromogenic) follows a schedule, based on the time from gene therapy infusion, at first weekly then with reduced frequency.
- Duration of expression

Patient reported outcomes

- Chronic pain
- Mental health

Healthcare resource utilization: including hospitalization, emergency room visits, factor IX utilization, adjunctive medication (e.g. tranexamic acid, medications), homecare services, specialty consultations.

Safety outcomes

- Mortality/ cause of death
- Liver toxicity; short-term immune response to factor; thrombosis; vector integration into host genome; duration of vector-neutralizing response; other long-term adverse events

In addition, the following outcomes are crucial in assessing treatment response in routine clinical practice:

- Ability to discontinue routine prophylaxis with minimal breakthrough bleeds: routine prophylaxis is defined as continuous replacement with standard CFCs or non-factor therapy for a minimum of 48 out of 52 weeks per week, with the intent to prevent bleeding. This information is routinely collected in the Canadian Bleeding Disorders Registry (CBDR), and updated annually or more frequently by the HTC.
- Reduced annualized factor utilization: This includes factor utilization for routine prophylaxis, episodic treatment for acute bleeds and trauma, and surgical/situational prophylaxis. This information is routinely collected by patients/families on the MyCBDR portal, and available to clinicians and relevant stakeholders (e.g. AHCDC, Canadian Blood Services)

- Improved joint health: presence of target joints (a single joint with 3 or more spontaneous bleeds in a 6-month period), hemophilic arthropathy as assessed by standardized instrument such as the HJHS score. Joint health is routinely assessed during annual comprehensive hemophilia assessments by physiotherapists.

- Patient reported outcomes using validated generic and disease-specific questionnaires: health-related quality of life, treatment burden, treatment satisfaction, work and school absenteeism, and measures of physical activity. These measures are not routinely collected. Gene therapy participants and treating centres are strongly encouraged to enroll patients to the WFH gene therapy registry, and participate in the collection of the core outcome set including patient-reported outcomes in addition to routinely collected clinical information.

Treatment response including use of prophylaxis, annualized factor utilization, annualized bleeding rates, and joint health are formally assessed on an annual basis. However, as patients record their bleeding diaries and factor/ non-factor product utilization in real-time, any clinical changes will be flagged and reviewed sooner by members of the hemophilia multidisciplinary healthcare teams. The factor IX activity will be measured regularly, the frequency based on timing from gene therapy infusion. The frequency will follow the protocol as per the clinical trial protocol and drug monograph, and also depends on the trend of serial factor IX activities.

A clinically meaningful response may include one or more of the following:

- For patients on prophylactic replacement, **the ability to discontinue routine prophylactic therapy**. Of note, some patients may still require episodic prophylaxis during times of high-risk for bleeding, such as factor prophylaxis during times of major surgeries or trauma.

- **Reduction in the annualized utilization of CFCs or non-factor products**

- Low annualized bleeding rates: zero or near-zero spontaneous annualized bleeding rates including all bleeds and bleeds into the index joints.

- Sustained expression of FIX activity: factor IX activity does not always correlate with the bleeding tendency or need for prophylactic therapy. While severe hemophilia is characterized by recurrent bleeds requiring routine prophylaxis, moderate hemophilia (0.01-<0.05 IU/ml) is a more heterogenous group. Some persons with moderate hemophilia (e.g. factor 0.01-0.02 IU/ml) may behave like those with severe hemophilia and require routine prophylactic replacement, while others may rarely bleed outside of traumatic or surgical settings. As a result, factor IX activity should only be used as a secondary outcome. For instance, for an individual with baseline factor IX of 0.01 IU/ml requiring long-term prophylaxis to prevent recurrent bleeds, the ability to discontinue prophylaxis with near-zero bleeds over the next 5-10 years would be considered a clinical meaningful response even if factor IX is only 0.04 IU/ml in year 10. The limitation of factor IX levels is further emphasized by substantial discrepancies in quantitating factor IX by different commonly used factor IX activity assays.

- Improvement in patient reported outcomes including health-related quality of life, chronic pain and treatment burden.

The magnitude of treatment response would not vary across multidisciplinary healthcare professionals involved in the assessment and care of PWH.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Gene therapy is a one-time treatment. Criteria for treatment discontinuation is not relevant for the drug under review.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

A “hub and spoke model” of gene therapy implementation and delivery has been proposed by a joint publication by the European Association for Haemophilia and Allied Disorders (EAHAD) and the European Haemophilia Consortium and adopted by Quebec with success [10, 11]. The current strategy from the AHCDC is to adopt the proposed “hub and spoke model” with appropriate adaptation to Canadian needs. The model is characterized by a close collaboration and communication between gene therapy dosing centres

("hubs") and referral/follow-up centres ("spokes"). Empirically, the model has shown to perform efficiently and safely for enrollment of approximately 10 patients in gene therapy trials, whereby most patients were infused in a few clinical centers, and followed up in "spoke" centers. All referral/follow-up centres belong to one of the 26 hemophilia treatment centres (HTCs). The local HTC clinic director will be responsible for the diagnosis, identification and screening of eligible patients, education and counselling, and post-infusion follow-up care. Once interested patients meet the eligibility criteria and are deemed a suitable candidate, they will be referred to one of the regional gene therapy dosing centres. The dosing centres include HTCs that have participated in or are selected to participate in gene therapy clinical trials as well as other HTCs with the resources and infrastructure to serve as an infusion site. The AHCDC, in collaboration with individual HTCs, is in the process of selecting a list of gene therapy dosing sites over the next year. Attention to geographic distribution will be paid to ensure equitable access to all Canadians.

Patients will travel to the closest regional gene therapy dosing site for infusion. Treatment will be delivered in a monitored setting in a tertiary hospital, which will ensure safe product storage and handling, safe area for containment, supplies and trained personnel for handling infusion reactions. Following initial treatment, patients will be monitored closely by their local HTC. The dosing site will continue to act as a consultant and provide expert advice, if needed, to support ongoing monitoring and treatment.

Other than hemophilia clinic directors, other specialties that may be involved in the care of patients undergoing gene therapy include:

1) Psychologists, psychiatrists, or counsellors: to provide psychosocial assessment and support throughout the patient journey pre- and post-infusion of gene therapy

2) Hepatologists: to assess baseline liver function to help determine eligibility (e.g. arrange liver ultrasound with elastography to assess baseline liver fibrosis or steatosis), assess and manage transaminitis that may occur following infusion.

3) Social workers/ occupational therapists: to assist with social, financial, and logistic support for patients and families throughout the journey.

4) Home care: to assist with sample collection in patients who live in rural/remote regions, and/or have barriers to frequent visits to the hospital laboratory for monitoring.

6. Additional Information

References:

1. Iorio, A., Stonebraker, J. S., Chambost, H., Makris, M., Coffin, D., Herr, C., & Germini, F. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males. Annals of Internal Medicine. 2019; 171(8): 540. https://doi.org/10.7326/M19-1208

2. Canadian Hemophilia Registry. "Factor FIX Deficiency-2020". https://fhs.mcmaster.ca/chr/pdf/20/FIX%202020.pdf

3. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, Carcao M, Mahlangu J, Ragni MV, Windyga J, Llinás A, Goddard NJ, Mohan R, Poonnoose PM, Feldman BM, Lewis SZ, van den Berg HM, Pierce GF; WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26 Suppl 6:1-158.

4. Buckner TW, Witkop M, Guelcher C, Sidonio R, Kessler CM, Clark DB, Owens W, Frick N, Iyer NN, Cooper DL. Impact of hemophilia B on quality of life in affected men, women, and caregivers-Assessment of patient-reported outcomes in the B-HERO-S study. Eur J Haematol. 2018;100(6):592-602.

5. Steen Carlsson K, Winding B, Astermark J, Baghaei F, Brodin E, Funding E, Holmström M, Österholm K, Bergenstråle S, Lethagen S. High use of pain, depression, and anxiety drugs in hemophilia: more than 3000 people with hemophilia in an 11-year Nordic registry study. Res Pract Thromb Haemost. 2023 Jan 31;7(2):100061.

6. Nguyen NAT, Auquier P, Beltran Anzola A, d'Oiron R, Biron-Andréani C, Lienhart A, Rauch A, Baumstarck K, Boucekine M, Milien V, Rosso-Delsemme N, Tabele C, Giraud N, Sannié T, Chambost H, Resseguier N; INTHEMO Study Group. Occupational

integration of adults with severe haemophilia (INTHEMO): A study based on the FranceCoag registry. Haemophilia. 2022;28(6):962-976.

7. Plug I, Peters M, Mauser-Bunschoten EP, de Goede-Bolder A, Heijnen L, Smit C, Willemse J, Rosendaal FR, van der Bom JG. Social participation of patients with hemophilia in the Netherlands. Blood. 2008;111(4):1811-5.

8. Krumb E, Lambert C, Hermans C. Patient selection for hemophilia gene therapy: real-life data from a single center. Res Pract Thromb Haemost 2021; 5: 390–394.

9. Iorio A, Skinner MW, Clearfield E, Messner D, Pierce GF, Witkop M, Tunis S; coreHEM panel. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. Haemophilia. 2018;24(4):e167-e172.

10. Miesbach W, Chowdary P, Coppens M, et al. Delivery of AAV-based gene therapy through haemophilia centres-A need for re-evaluation of infrastructure and comprehensive care: a Joint publication of EAHAD and EHC. Haemophilia. 2021;27(6):967-973.

11. Personal communications, Dr. Molly Warner.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   AHCDC received no help from outside our clinician group to complete the submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.
3. AHCDC received no help from outside our clinician group to collect or analyze any information used in this submission.

4. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Haowei (Linda) Sun
Position: Chair, Novel Therapy Committee, AHCDC; Hemophilia Clinic Director, Northern Alberta Bleeding Disorders Program; Associate Professor, Division of Hematology, Department of Medicine, University of Alberta
Date: 05-10-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Pfizer	X			
Roche	X			
Sanofi	X			
Takeda/ Shire	X			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Jerry Teitel
Position: Past president, AHCDC; Member, AHCDC Novel Therapy Committee; Professor, Division of Hematology, Department of Medicine, University of Toronto
Date: 05-10-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Pfizer	X			
Roche	X			
Sanofi	X			
Takeda	X			
Biomarin		X		
Vega Therapeutics		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Alfonso Iorio
Position: Professor, Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University; Co-chair of the World Federation of Haemophilia (WFH) World Bleeding Disorder Registry; Past Chair of the WFH Data and Demographics Committee

Date: Aug-14-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer			X	
Roche				X
Takeda				X
Spark			X	
Bayer				X
Sanofi		X		
Sobi				X

* Place an X in the appropriate dollar range cells for each company.

Note: **No money was received personally by myself from any pharma company**. The dollar ranges indicated below are for research contracts (e.g. conduct of clinical trials) or research service agreements (e.g. data analysis) paid from sponsors to Hamilton Health Sciences or McMaster University. All research relationships have been disclosed, irrespectively of the sponsor involvement with gene therapy trials or research.

Declaration for Clinician 4

Name: Dr. Adrienne Lee
Position: AHCDC executive board of directors; Member, AHCDC Novel Therapy Committee
Date: 05-10-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Takeda	X			
Pfizer	X			
Leo Pharma	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Victor Blanchette
Position: Hemophilia Clinic Director, Hospital for Sick Children; Member, AHCDC Novel Therapy Committee; Professor, Department of Pediatrics, University of Toronto
Date: 05-10-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Takeda		X		
Sanofi	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Mark Belletrutti
Position: Hemophilia Clinic Director, British Columbia Children's Hospital; Member, AHCDC Novel Therapy Committee; AHCDC executive board of directors
Date: <10-08-2023>

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche Canada		X		
Takeda Canada	X			
Bayer Canada	X			
Sanofi Canada	X			
Octapharma Canada	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Roy Khalife
Position: Member, AHCDC Novel Therapy Committee; AHCDC executive board of directors
Date: 05-10-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer Canada	X			
Takeda	X			
Novo Nordisk	X			

Bayer Canada	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Roona Sinha
Position: President, AHCDC
Date: 05-10-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Thrombosis Canada	X			
Canadian Blood Services Board of Directors	X			
Bayer	X			
Takeda/Shire	X			
Octapharma	X			

* Place an X in the appropriate dollar range cells for each company.