Canadian Journal of Health Technologies
March 2024 Volume 4 Issue 3

CADTH Reimbursement Recommendation

Fidanacogene Elaparvovec (Beqvez)

Indication: For the treatment of adults (aged 18 years or older) with moderately severe to severe hemophilia B (congenital Factor IX deficiency) who are negative for neutralizing antibodies to variant AAV serotype Rh74

Sponsor: Pfizer Canada ULC

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Beqvez?

CADTH recommends that Beqvez be reimbursed by public drug plans for the treatment of adults with moderately severe to severe hemophilia B (congenital factor IX deficiency) who are negative for neutralizing antibodies to variant adeno-associated virus (AAV) serotype Rh74 , if certain conditions are met.

Which Patients Are Eligible for Coverage?

Beqvez should only be covered to treat adult patients (aged 18 years or older) with circulating coagulation factor IX (FIX:C) activity of 2% or less and bleeding that requires ongoing prophylactic treatment. Beqvez should not be covered if the patient has FIX inhibitors or has previously received gene therapy for hemophilia B.

What Are the Conditions for Reimbursement?

Beqvez should only be reimbursed if prescribed by specialists who have expertise in treating hemophilia B and if the cost of Beqvez is reduced. Beqvez is a 1-time therapy.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Beqvez decreased annualized bleeding rates and reduced the use of FIX compared to routine FIX prophylaxis in adult male patients with moderately severe to severe hemophilia B.
- Beqvez meets additional needs that are important to patients because it is a 1-time gene therapy that can restore coagulation factors to clinically effective levels.
- Based on CADTH's assessment of the health economic evidence, Beqvez does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Beqvez is estimated to cost the public drug plans approximately $127 million over the next 3 years. The estimated budget impact is highly sensitive to the number of patients eligible to receive Beqvez.
- The implementation of Beqvez may raise ethical and equity considerations related to access because of the resource-intensive nature of gene therapy and the currently limited number of infusion centres across Canada.

Summary

Additional Information

What Is Hemophilia B?

Hemophilia B is a life-long genetic bleeding disorder resulting from a deficiency in FIX that leaves patients at risk for excessive blood loss and organ damage. As of 2021, there were more than 700 patients with hemophilia B in Canada.

Unmet Needs in Hemophilia B

There is a need for treatments for hemophilia B that will alter the underlying disease process, restore coagulation factors to clinically effective levels, reduce the need for venipunctures, prevent or reduce bleeds, and improve quality of life.

How Much Does Beqvez Cost?

Treatment with Beqvez is expected to cost $4,773,595 per patient.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that fidanacogene elaparvovec be reimbursed for the treatment of adults (aged 18 years or older) with moderately severe to severe hemophilia B (congenital factor IX deficiency) who are negative for neutralizing antibodies (nAbs) to variant adeno-associated virus (AAV) serotype Rh74 (AAVRh74var), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

CDEC recognized the rarity of hemophilia B and the unmet needs of patients with this disease who require coagulation factor IX (FIX) prophylaxis. Evidence from a phase III, single-arm, open-label clinical trial (the BeneGene-2 trial) demonstrated that treatment with fidanacogene elaparvovec decreased annualized bleeding rates and reduced the use of FIX in adult male patients with moderately severe to severe hemophilia B (circulating coagulation factor IX [FIX:C] ≤ 2%) compared to the same patients treated with routine FIX prophylaxis during a lead-in study (the BeneGene-1 study). After a median duration of follow-up of approximately [redacted], the difference in annualized bleeding rate for treated and untreated bleeds (ABR_{total}) between patients was −3.13 (95% confidence interval [CI], −5.44 to −0.81) at week 12 to month 15 (denoted as year 1) after fidanacogene elaparvovec infusion, favouring fidanacogene elaparvovec. Results for other bleeding outcomes (annualized bleeding rate for treated bleeds [ABR_{treat}] and annualized bleeding rate for treated and untreated joint bleeds [ABR_{joint}]) and the use of FIX (annualized infusion rate [AIR] and [redacted]) also showed a benefit with fidanacogene elaparvovec compared to FIX prophylaxis during the follow-up period.

Patients identified a need for treatments that alter the underlying disease process, restore coagulation factors to clinically effective levels, reduce the need for venipunctures, prevent or reduce bleeds, and improve their quality of life (QoL). CDEC concluded that fidanacogene elaparvovec may meet some of these needs because it is a 1-time gene therapy designed to provide an alternative active source of endogenous FIX that improves bleeding outcomes and reduces FIX use after treatment. The evidence from the BeneGene-2 trial is associated with uncertainty because the comparative evidence is nonrandomized and potential sources of bias were identified (e.g., open-label design, self-reported bleeding events, subjective nature of some outcomes, assumptions of the statistical models used for intrapatient comparisons). In addition, while patients are expecting gene therapy to be effective for at least 10 years, the long-term efficacy of fidanacogene elaparvovec is unknown due to the limited duration of follow-up in the available evidence.

Based on the sponsor's submitted analysis, fidanacogene elaparvovec may improve health outcomes and reduce overall health care costs relative to FIX prophylaxis. However, at the submitted price, it will take at least 12 years for the acquisition cost of fidanacogene elaparvovec to be offset by cost-savings to the health care system and be considered cost-neutral. There are limited data to support the long-term efficacy of fidanacogene elaparvovec. There is also a high degree of clinical uncertainty, and the potential for the scope of clinical practice to change during this period. Jurisdictions may wish to consider price reductions and/or other product listing mechanisms to mitigate the long-term financial risk to public payers.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults (aged ≥ 18 years) who meet all of the following criteria: 1.1. documented moderately severe to severe hemophilia B based on FIX:C ≤ 2% and bleeding requiring ongoing prophylactic treatment 1.2. Negative for neutralizing antibodies to variant AAV serotype Rh74.	The BeneGene-2 trial demonstrated that treatment with fidanacogene elaparvovec had a clinical benefit in adult patients who had moderately severe to severe hemophilia B, which was defined as circulating FIX:C ≤ 2%. Clinical experts indicated that disease severity should be based on FIX:C level as well as the patient's clinical phenotype and clinician judgment regarding their need for treatment to prevent bleeds. Patients were excluded if their anti-AAVRh74var nAb titre was ≥ 1:1.	Testing for anti-AAVRh74var nAb will be required before infusion of fidanacogene elaparvovec.
2. Fidanacogene elaparvovec should not be reimbursed in patients who meet any of the following criteria: 2.1. presence of factor IX inhibitors 2.2. previous receipt of gene therapy for the treatment of hemophilia B.	Patients were excluded from the BeneGene-2 trial if they had a prior history of FIX inhibitors or positive FIX-inhibitor testing, defined as ≥ 0.6 BU. Patients previously dosed with a gene therapy were excluded from the BeneGene-2 trial. Clinical experts noted that if a gene therapy uses an AAV vector, patients will develop nAbs against the AAV vector after treatment.	In cases of a positive test for alloantibodies against factor IX, a retest within approximately 2 weeks should be performed. If both the initial test and retest results are positive, the patient should not receive fidanacogene elaparvovec.
Renewal		
3. Treatment with fidanacogene elaparvovec is a 1-time therapy.	Fidanacogene elaparvovec is administered as a single dose, and gene therapy re-treatment has not been established as an efficacious strategy at this time.	—
Prescribing		
4. Fidanacogene elaparvovec must be prescribed by specialists who have expertise in treating hemophilia B.	This is to ensure fidanacogene elaparvovec is prescribed for the most appropriate patients, and that adverse effects are managed appropriately.	Fidanacogene elaparvovec should be prescribed based on the judgment of a multidisciplinary team, which is organized by a hemophilia comprehensive treatment centre and may consist of specialists such as a hematologist with experience in treating hemophilia patients, a physiotherapist to assess joint function, a hepatologist for liver-related issues, a pharmacist, and an HIV specialist if the patient is HIV-positive.
Pricing		
5. A reduction in price.	The committee noted that, due to the high degree of uncertainty regarding long-term efficacy, a price reduction is required. Although the sponsor's submitted analysis suggests fidanacogene elaparvovec may	—

Reimbursement condition	Reason	Implementation guidance
	improve health and reduce overall health care costs relative to FIX prophylaxis, this result was based on uncertain assumptions concerning long-term efficacy. Based on the sponsor's submitted analysis, it will take at least 12 years for the acquisition cost of fidanacogene elaparvovec ($4,773,595) to be sufficiently offset by cost-savings to the health care system to be considered cost-effective at a $50,000 per QALY threshold. Price reductions of at least 57% and 17% would be required for fidanacogene elaparvovec to be considered cost-effective after 5 years and 10 years, respectively, using assumed prices for FIX prophylaxis. Further price reductions would be required if the treatment efficacy of fidanacogene elaparvovec were not sustained indefinitely, or if the prices paid for FIX prophylaxis were lower than assumed.	
Feasibility of adoption		
6. The feasibility of adoption of fidanacogene elaparvovec must be addressed.	At the submitted price, the incremental budget impact of fidanacogene elaparvovec is expected to be greater than $40 million in years 1 and 2.	—
7. The organizational feasibility of conducting anti-AAVRh74var nAbs testing must be covered by the sponsor.	Anti-AAVRh74var nAbs testing is required to determine eligibility for fidanacogene elaparvovec. The sponsor has indicated that they will cover costs related to neutralizing antibody testing.	—

AAV = adeno-associated virus; AAVRh74var = adeno-associated virus serotype Rh74; BU = Bethesda unit; FIX = coagulation factor IX; FIX:C = circulating coagulation factor IX; nAb = neutralizing antibody; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet needs:** Due to the uncertainty associated with the submitted evidence, CDEC deliberated on fidanacogene elaparvovec considering the criteria for significant unmet needs described in section 9.3.1 of *Procedures for CADTH Reimbursement Reviews*. CDEC noted that hemophilia B is a rare and severe disease, and the committee concluded that the limitations and uncertainty of the evidence were balanced with the significant unmet needs and rarity of the condition. Overall, CDEC concluded that the available evidence reasonably suggests that fidanacogene elaparvovec has the potential to reduce bleeding rates and use of FIX prophylaxis.
- **Need for new treatments:** CDEC discussed which patients with hemophilia B have the greatest need for gene therapy to treat their disease. In consultation with clinical experts, CDEC considered that

patients with FIX:C levels less than or equal to 2% and bleeding history should be prioritized; followed by those with FIX:C levels less than or equal to 2% and receiving FIX prophylaxis that controls their bleeding; then those with FIX:C levels greater than 2% with a bleeding history; then those with FIX:C levels greater than 2% and receiving FIX prophylaxis; then those with FIX:C levels greater than 2% who have no bleeding history or are receiving FIX prophylaxis; then patients without bleeding or treatment experience.

- **Supportive results:** In the BeneGene-2 trial, results of FIX activity levels suggested that the steady-state FIX:C level for the majority of patients was higher than the prespecified fixed threshold of 5% and remained stable. Results for other bleeding outcomes (i.e., ABR_{treat}, ABR_{joint}, [redacted]) were consistent with ABR_{total}, favouring fidanacogene elaparvovec over FIX prophylaxis.
- **Long-term efficacy and safety**: According to the patient group input, most patients indicated that they would expect a gene therapy to be effective in preventing bleeding for at least 10 years. Similarly, clinical experts noted that a longer follow-up of 20 years to 25 years is warranted to definitively determine the long-term efficacy of fidanacogene elaparvovec. Therefore, an important limitation in the efficacy results in the pivotal BeneGene-2 trial was the relatively short duration of follow-up ([redacted]). To address this gap, evidence from a phase I/IIa, single-arm, open-label trial (Study C0371005) and a corresponding extension study (Study C0371003) that provided data for up to 6 years of follow-up was examined. In Study C0371003, the duration of follow-up ranged from [redacted] after fidanacogene elaparvovec infusion with only 5 participants having completed the 6-year, longer-term follow-up as of the data cut-off. However, the limitations of these supportive studies (e.g., single-arm and noncomparative design, descriptive analyses, small sample size, many patients with ongoing follow-up, missing data) precluded CDEC from drawing conclusions with certainty about the longer-term efficacy and safety of fidanacogene elaparvovec based on this evidence. Overall, CDEC determined that the long-term efficacy and safety of fidanacogene elaparvovec remains inconclusive.
- **Additional patient needs:** Patients indicated that they hope gene therapy would lead to less stress and fewer restrictions on activities, and make it easier to travel, but CDEC could not definitively conclude that fidanacogene elaparvovec would meet these needs based on the submitted evidence. Similar to the patient group, the clinical experts consulted by CADTH noted that monitoring changes in Hemophilia Joint Health Score (HJHS) as well as health-related quality of life (HRQoL) are important for assessing treatment response. Although HRQoL was assessed in the BeneGene-2 trial using the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL), this evidence was noncomparative and therefore no conclusions could be drawn by CDEC regarding the effects of fidanacogene elaparvovec on this outcome. Similarly, effects on activities were assessed by the Haemophilia Activities List (HAL) but data were noncomparative. Although the Haem-A-QoL and HAL were also assessed in the single-arm Study C0371005 and Study C0371003, data were available for only 4 patients, thus further limiting the interpretation of those results. As such, no conclusions could be drawn regarding the effect of fidanacogene elaparvovec on HRQoL and patients' activities.
- **Number of eligible patients:** CDEC discussed the uncertainty in the number of patients with moderately severe to severe hemophilia B in Canada eligible for fidanacogene elaparvovec. Clinical

experts consulted by CADTH indicated that clinical phenotype is used to determine a patient's disease severity and treatment, not a cut point of FIX:C of 2%, which was used as an enrolment criterion in the BeneGene-2 trial. Experts estimate that up to 50 patients in Canada may receive fidanacogene elaparvovec in the next 3 years. Should the total number of patients with moderately severe to severe hemophilia B be larger or uptake of fidanacogene elaparvovec be higher than estimated by the sponsor, the budget impact of reimbursing fidanacogene elaparvovec will be greater.

- **Uncertainty in the economic evaluation:** CDEC discussed the uncertainty in the economic analysis, specifically that in the absence of robust comparative evidence, the incremental gain in quality-adjusted life-years (QALYs) with fidanacogene elaparvovec predicted in the sponsor's analysis may overestimate the incremental benefits relative to FIX prophylaxis. The majority of benefits associated with fidanacogene elaparvovec (93% of incremental QALYs) were accrued after the duration of the BeneGene-2 trial and rely on assumptions about sustained long-term benefit relative to FIX prophylaxis.
- **Neutralizing antibody testing:** CDEC discussed that anti-AAVRh74var neutralizing antibody (nAb) testing would be required to determine eligibility for fidanacogene elaparvovec. The sponsor anticipates that the cost of testing will be [redacted] per patient tested and that 48% of patients tested will have nAbs (and thus be ineligible for fidanacogene elaparvovec).
- **Ethical and equity considerations**: CDEC discussed ethical and equity considerations for fidanacogene elaparvovec, including the high burden of care posed by FIX prophylaxis, which may leave patients susceptible to breakthrough bleeds and require restricting daily activities. The committee noted that females may experience disparities in access to care, including for gene therapy, as they may be underrecognized or underdiagnosed as living with hemophilia. The committee discussed that a strictly FIX-based eligibility criterion was inconsistent with clinical practice and as potentially limiting equitable access for some patients who could benefit from fidanacogene elaparvovec, were it reimbursed. As a 1-time therapy that cannot be terminated once infused, the committee highlighted the importance of robust informed consent and establishing reasonable expectations regarding long-term effectiveness. The committee discussed the importance of addressing potential geographic barriers to equitable access, given the limited number of infusion centres in Canada. CDEC also discussed how the high cost of the therapy challenges health care system sustainability, and noted the possible role that alternative funding models may play in the fair distribution of risks and benefits associated with reimbursing a high-cost therapy with uncertain long-term effectiveness. Given the high costs, uncertainty about which patients are most likely to benefit, and possibility for vector production shortages, the committee discussed the potential need to develop clear, fair prioritization criteria.

Background

Hemophilia is a serious, X-linked, life-long genetic disorder that leaves patients at increased risk of blood loss and organ damage due to impaired functioning of the coagulation cascade. Hemophilia B is

characterized by an absence or shortage of FIX resulting from a mutation in the *F9* gene. Moderate and severe hemophilia B cases are defined by the World Federation of Hemophilia (WFH) as having 1% to 5% and less than 1% of normal enzymatic FIX activity, respectively. However, according to the clinical experts consulted by CADTH, severity in clinical practice is defined by a patient's phenotype (i.e., tendency to bleed) and not simply their factor activity levels; the decision to initiate prophylaxis with clotting factor concentrates takes into the account their clinical phenotype and factor activity levels, as well as lifestyle and professional activities. Individuals with moderately severe to severe hemophilia frequently experience bleeding and recurrent spontaneous bleeding events into muscle, soft tissue, and joints (hemarthroses). Hemarthrosis is the most common manifestation of moderate and severe hemophilia B. As of 2021, there were 704 patients with hemophilia B (with recorded severity) in Canada, 535 of whom were adult male patients.

The treatment goal for hemophilia, as outlined by the WFH guidelines, is to reduce or prevent bleeding while allowing patients to lead active lives and experience a QoL comparable to individuals not affected by the condition. Current management strategies for hemophilia B include on-demand treatment to stop bleeds as they occur and/or routine prophylaxis therapy to prevent bleeding, both involving the administration of exogenous FIX coagulation factor concentrates (CFCs) to treat the FIX deficiency.

Fidanacogene elaparvovec is an AAV vector-based gene therapy indicated for the treatment of adults (aged 18 years or older) with moderately severe to severe hemophilia B (congenital factor IX deficiency) who are negative for neutralizing antibodies to variant AAV serotype Rh74. It is available as 1×10^{13} vector genomes (vg)/mL, and the dosage recommended in the product monograph is 5×10^{11} vg/kg of body weight administered as a single-dose IV infusion.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 pivotal phase III, open-label, single-arm clinical study (along with a lead-in study conducted before the pivotal study to provide a comparator) in male participants (aged ≥ 18 years) with moderately severe to severe hemophilia B (defined as FIX:C ≤ 2%), and 1 additional study (along with a lead-in study) addressing gaps in the systematic review evidence
- patient perspectives gathered by 1 patient group, the Canadian Hemophilia Society (CHS)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- a panel of 4 clinical specialists with expertise diagnosing and treating patients with hemophilia B
- input from 2 clinician groups, including the Association of Hemophilia Clinic Directors of Canada (AHCDC) and Canadian Association of Nurses in Hemophilia Care (CANHC)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related fidanacogene elaparvovec from published literature.

Stakeholder Perspectives

Patient Input

The CHS provided input for the review of fidanacogene elaparvovec for the treatment of moderately severe to severe hemophilia B patients aged 18 years or older. Patient input was gathered from an online survey, conducted between July 10, 2023, and July 31, 2023. In total, 17 responses were gathered by the CHS. All respondents were affected by severe or moderately severe hemophilia B without inhibitors. In addition, in September 2022, the CHS conducted an online survey of people living in Canada with severe hemophilia A and B and received 39 responses; among them, 31 were individuals with hemophilia A, 7 with hemophilia B, and 1 not specified.

Joint damage — primarily to knees, ankles, and elbows, caused by repeated internal hemarthroses — was reported to be the primary physical health impact of hemophilia B. Regarding the currently available treatments, 4 patients reported being very satisfied, 7 satisfied, 5 neither satisfied nor dissatisfied, and 1 very dissatisfied. Patients from this survey noted that treatments greatly complicate their everyday life, travel, and leisure activities. They also mentioned the difficulty with infusion due to vein visibility, poor vein issues, and side effects. Patients also reported socioeconomic problems they face due to regular visits, such as missing work due to visits, travel and insurance issues, and access issues.

When patients from the 2023 CHS survey were asked how gene therapy could potentially change their lives, all patients provided positive feedback. Patients hoped gene therapy would lead to fewer FIX infusions, minimal needle injections, less stress, less bleeding, and fewer restrictions on activities, and make it easier to travel. In addition, approximately 63% of the respondents from the 2022 survey indicated they expected gene therapy to be effective in preventing bleeding for at least 10 years. The 2022 survey asked if people would receive gene therapy knowing that there would be frequent blood draws in the weeks and months following administration, and that they would need to be followed up in a registry for 10 to 20 years. In response, 66% answered yes, 10% answered no, and 24% indicated that they did not know.

The CHS mentioned that a small number of people living in Canada (likely close to 5) have undergone gene therapy for hemophilia B, but nothing is known to the CHS about their experience outside the preliminary data from the trials.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH noted that FIX prophylaxis requires frequent IV injections conducted by the patients themselves, which poses a heavy burden for patients with hemophilia B and significantly impacts patients' ability to live a normal life. The clinical experts consulted by CADTH noted that poor adherence to FIX prophylaxis may result in reduced effectiveness and increased risk of bleeding, and even patients who execute prophylaxis on the prescribed schedule (i.e., are adherent) can experience breakthrough bleeds, particularly in the days before the next infusion. According to the clinical experts consulted by CADTH, the key advantage of fidanacogene elaparvovec over exogenous FIX prophylaxis

regimen, if effective, would be avoiding the fluctuation of FIX levels and eliminating the need for repeated CFC infusions. The clinical experts consulted by CADTH noted that fidanacogene elaparvovec could be a curative treatment if a steady high level of FIX is expressed and efficacy is maintained long-term. The clinical experts consulted by CADTH noted that it remains uncertain whether the use of fidanacogene elaparvovec will cause a shift in treatment paradigm.

The clinical experts noted that all patients with hemophilia B who have clinically severe phenotype regardless of FIX level are likely to benefit from treatment with fidanacogene elaparvovec in terms of reductions in burden of care, pain, and pain interference, as well as improvement in mobility and quality of life. The clinical experts noted that those who would likely benefit the most from the treatment of fidanacogene elaparvovec would be patients without pre-existing joint damage due to hemophilia B, as well as younger patients who are usually more active. The clinical experts consulted by CADTH noted that the identification of patients best suited for treatment should be through clinical assessment and shared decision-making with patients. Based on the study design of the pivotal BeneGene-2 trial, the clinical experts indicated that testing for nAb against AAVRh74var capsid should be mandatory to receive fidanacogene elaparvovec. The clinical experts consulted by CADTH noted that patients least suitable for fidanacogene elaparvovec include those with pre-existing antibodies against AAV and those who consider that the benefit does not outweigh the risk associated with fidanacogene elaparvovec gene therapy, in that its long-term efficacy and safety remain unclear. In addition, some patients may not want to change their current treatment.

According to the clinical experts consulted by CADTH, the most important assessment for treatment response is to monitor patients' bleeding to observe whether fidanacogene elaparvovec prevents bleeding events and allows patients to live the lifestyle they want without concern for risk of bleeding. The clinical experts agreed that the length of follow-up for hepatic function and FIX activity levels after infusion of fidanacogene elaparvovec should be life-long. The clinical experts noted that the postinfusion monitoring of fidanacogene elaparvovec will be more frequent for the short term, and less frequent over time for the long term. The clinical experts consulted by CADTH noted that it is reasonable to monitor FIX activity level and liver function tests twice a week at the early stages after infusion, although the production of FIX is unlikely to happen immediately after infusion. The clinical experts noted that monitoring changes in HJHS as well as in QoL–related end points after infusion of fidanacogene elaparvovec (e.g., improvement in activities of daily living, physical activity, and functioning; decrease in development of disability; and improvement in psychosocial health and functioning) are also important. The clinical experts consulted by CADTH noted that the determination of treatment failure should be case-by-case, based on the judgment of the treating clinician. The clinical experts consulted by CADTH noted that if fidanacogene elaparvovec fails, patients may not be eligible for another gene therapy developed based on AAV vectors because they may present cross-reactivity against most AAV vectors.

The clinical experts consulted by CADTH noted that fidanacogene elaparvovec should be prescribed based on the judgment of a multidisciplinary team that is composed by a hemophilia comprehensive treatment centre, and may consist of specialists such as a hematologist with experience in treating patients with hemophilia, a physiotherapist to assess joint function, a hepatologist for liver-related issues, pharmacy support, and an HIV specialist (if the patient is HIV-positive). The clinical experts noted that the

administration of fidanacogene elaparvovec is on an outpatient basis, as is follow-up after fidanacogene elaparvovec infusion for most patients.

Clinician Group Input

A total of 9 clinicians from AHCDC and 3 nurses from CANHC provided input. Both AHCDC and CANHC highlighted that the currently available treatments in Canada do not modify or alter the underlying disease process, hence making persons with hemophilia B dependent, life-long, on regular IV infusions of FIX to prevent and treat bleeding. In addition, AHCDC noted that the frequent venipuncture required for prophylactic CFC replacement can pose challenges for patients with poor venous access. The group emphasized that all of these factors lead to the need for persons with hemophilia B and a severe bleeding phenotype to restore coagulation factor to clinically effective levels without the need for frequent venipunctures on a regular basis throughout one's lifespan. AHCDC also mentioned the variability of the efficacy of prophylaxis with CFCs across individuals, which poses some patients susceptible to breakthrough bleeds into joints and muscles.

Both AHCDC and CANHC noted that fidanacogene elaparvovec would provide a 1-time treatment leading to sustained FIX production, thus addressing the underlying disease process and natural history, rather than symptomatic management. This would represent a paradigm shift in the treatment of hemophilia B. AHCDC indicated that eligible candidates for gene therapy include adults with hemophilia B with clinically severe bleeding phenotype requiring prophylaxis, no history of inhibitory antibodies, no significant comorbidities, and no pre-existing anti-AAV nAbs.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The current standard of care for those with moderately severe or severe hemophilia B is routine prophylaxis, involving the regular IV administration of FIX (BeneFIX, Alprolix, Rebynin, and Immunine VH). There is no direct gene therapy comparator product in the marketplace.	This is a comment from the drug plans to inform expert committee deliberations.
Are vendor-supplied real-world evidence and indirect treatment comparison studies appropriate to confirm better clinical outcomes for fidanacogene elaparvovec compared with available FIX?	The sponsor did not submit real-world evidence or an indirect treatment comparison for this review. The sponsor submitted a single-arm, phase III pivotal trial, which included comparisons to a lead-in study. The sponsor also submitted a phase II trial with an associated lead-in study to address the gap in longer-term impact.
The comparators in the sponsor's submission are recombinant FIX products supplied by CBS for the management of moderately severe to severe hemophilia B in adults in Canada (excluding Quebec).	This is a comment from the drug plans to inform expert committee deliberations.

Implementation issues	Response
If fidanacogene elaparvovec is funded by the public drugs plans there would need to be coordination between the public drug plans and CBS (i.e., prophylactic dose of one of the comparators is given before infusion with fidanacogene elaparvovec). These treatments are provided at no cost to the patient (i.e., no deductibles or copays). If the comparators are considered under public drug plans, they would have to meet the eligibility requirements which would also include copays in certain jurisdictions. In addition, there will likely be travel expenses.	
What is the timing between prophylaxis and infusion of fidanacogene elaparvovec? What is the transition plan for patients moving from the comparator drug to this therapy?	The clinical experts consulted by CADTH noted that it does not matter when the last FIX prophylaxis is before infusion of fidanacogene elaparvovec. For a patient who is on FIX prophylaxis, the clinician can set a date for the patient to receive fidanacogene elaparvovec. Until that date, the patient can still have a FIX prophylaxis regimen. After the infusion of fidanacogene elaparvovec, it will take a period of time (e.g., 1 to 4 weeks) for fidanacogene elaparvovec to start producing transgenic FIX. The FIX prophylaxis regimen should continue during this period to avoid bleeds and provide protection.
Considerations for initiation of therapy	
The product monograph includes tests to confirm eligibility for fidanacogene elaparvovec and to ensure the safety and effectiveness. Tests include a liver fibrosis test, liver function tests, FIX inhibitor assay, blood test for the presence of chronic infections, and screening for nAb seropositivity against the specific AAVRh74var. In the event of a criteria-based recommendation for reimbursement, which marker(s) or criteria should be used to start therapy with fidanacogene elaparvovec?	The clinical experts consulted by CADTH noted that overall, many factors need to be considered before initiation of fidanacogene elaparvovec to identify patients who are likely to benefit from fidanacogene elaparvovec. The decision should be based on the judgment of the treating clinician via discussion with patients and their referring centres. The clinical experts consulted by CADTH noted that the pivotal BeneGene-2 trial provided several criteria, including patients' FIX level as well as status of nAbs against AAVRh74var, nAbs against FIX, and liver function. The clinical experts noted that in clinical practice, situations can be more complex. For instance, in addition to the FIX level, clinicians must take into account the clinical phenotype of the disease to determine the severity of disease.
Participants were excluded from the pivotal trial for reasons that may reduce the safety or efficacy of the infusion such as nAbs against AAVRh74var or history of or presence of nAbs against FIX (i.e., FIX inhibitors). Testing for nAbs against AAVRh74var is expected to be required to confirm eligibility for fidanacogene elaparvovec. Should patients excluded from the pivotal study due to reasons such as being nAbs against AAVRh74var–positive, or having a history or presence of nAbs against FIX, be eligible for fidanacogene elaparvovec? Is a program needed to identify eligible patients? If nAb testing is required for eligibility, is this a test that is available in each jurisdiction (all provinces and territories)?	The clinical experts consulted by CADTH noted that overall, nAb testing should be required to select patients eligible for fidanacogene elaparvovec. In terms of testing for nAbs against FIX (i.e., FIX inhibitors), the clinical experts noted that it is part of the standard of clinical practice in Canada. Clinicians will measure nAbs against FIX regularly. In addition, the clinical experts consulted by CADTH noted that it is reasonable to exclude a patient who has currently active nAbs against FIX, but noted that these antibodies are very rare in people with hemophilia B. In terms of testing for nAbs against AAVRh74var, the clinical experts consulted by CADTH noted that this should be a requirement for initiating fidanacogene elaparvovec. It is acceptable to exclude a patient who has anti-AAVRh74var nAb titre ≥ 1:1, a criterion used

Implementation issues	Response
(The sponsor indicated that they are planning an optional patient support program, which would offer nAb testing.)	in the pivotal BeneGene-2 trial, although there is still uncertainty in evidence associated with the titre threshold (≥ 1:1). The clinical experts consulted by CADTH noted that it remains unknown to them about the capacity for nAb testing against AAVRh74Var in Canada, and relevant issues (e.g., testing being done in the US through a support program offered by the sponsor, types of assays) should be further discussed with the sponsor.
The drug plans noted that eligible patients for the pivotal study would have already received rFIX therapy for hemophilia B, and are seeking information on how long patients need to have received comparator drugs before starting this therapy. Should it be a requirement for the patient to be on FIX therapy to receive fidanacogene elaparvovec? If yes, what is the duration of time they should be on FIX therapy before receiving fidanacogene elaparvovec?	Since hemophilia B is a congenital disease, the clinical experts reported that it is extremely unlikely that an adult patient candidate for gene therapy would have never received FIX in their life. An adult never being exposed to FIX may suggest that the patient's clinical phenotype is so mild that FIX prophylaxis is not needed. The clinical experts also noted that it is more precise to state fidanacogene elaparvovec should be given to patients who need FIX prophylaxis, rather than to those who have been on a FIX prophylaxis regimen.
Would there be a need to continue the comparator products after the 1-time IV infusion of fidanacogene elaparvovec?	The clinical experts consulted by CADTH noted that the comparator products (FIX prophylaxis regimens) will be needed until fidanacogene elaparvovec starts to work (probably 2 to 4 weeks after infusion). In addition, the clinical experts consulted by CADTH noted that the comparator products may also be needed when patients receive surgery after infusion of fidanacogene elaparvovec.
The indication specifies "moderately severe or severe hemophilia B." How should this be defined?	The clinical experts consulted by CADTH noted that using FIX:C ≤ 2% as the definition was acceptable from the perspective of conducting a clinical trial. However, from the perspective of daily clinical practice, the experts indicated that using this FIX level as a criterion for eligibility is not appropriate. Some patients' disease may be clinically severe despite having a level of FIX > 2%. Therefore, disease severity should be determined by the observation and judgment of clinicians in clinical practice.
Considerations for continuation or renewal of therapy	
Fidanacogene elaparvovec is indicated as a 1-time infusion. Would there be a situation where it would be needed or appropriate to administer a second treatment of fidanacogene elaparvovec?	The clinical experts consulted by CADTH noted the answer is no, because nAbs against AAVRh74var will be developed from the first treatment.
What objective markers should be used to assess initial and ongoing response to treatment? What follow-up will be required for patients treated with fidanacogene elaparvovec? How long should patients be monitored for hepatic function and FIX activity levels after infusion of fidanacogene elaparvovec?	The clinical experts consulted by CADTH noted that the most important assessment for treatment response is to monitor patients' bleeding. It can be considered a complete response if fidanacogene elaparvovec prevents bleeding and allows patients to live the lifestyle they want without concern for risk of bleeding. The clinical experts consulted by CADTH noted that FIX activity level should also be monitored. Monitoring FIX activity level allows clinicians to determine whether the deficiency in FIX has been corrected by fidanacogene elaparvovec. The clinical experts consulted by CADTH also noted that, in general, better FIX activity level is associated with better bleeding outcomes (e.g., no bleeding). However, in some cases, there is a discrepancy between FIX activity level and bleeding outcomes. There are also discrepancies in FIX

Implementation issues	Response
	levels measured using different assay methodologies. The clinical experts consulted by CADTH noted that follow-up should focus on both efficacy and safety through clinical follow-ups (e.g., checking patients' bleeding events and joint status via phone or virtual check-up) and lab tests (e.g., liver enzymes, FIX activity levels, and liver ultrasound to detect potential carcinomas). The clinical experts consulted by CADTH noted that the length of follow-up for hepatic function and FIX activity levels after infusion of fidanacogene elaparvovec should be life-long. In terms of frequency, the postinfusion monitoring of fidanacogene elaparvovec will be more frequent for the short term (e.g., for the first 3 months after infusion, lab tests mainly for liver enzymes and FIX level twice a week, starting around week 3 after infusion, or lab tests twice weekly initially and then once weekly), and less frequent over time for the long term (e.g., after the first 3 months, quarterly visit for the balance of the first year and then yearly visits life-long, or monthly visit for the balance of the first year and then only as clinically indicated). The clinical experts consulted by CADTH noted that tests for FIX level may not start immediately after infusion of fidanacogene elaparvovec, given that the production of FIX by fidanacogene elaparvovec is unlikely to happen immediately after infusion, although it is reasonable to monitor FIX activity level and liver function tests twice a week in the early stages after infusion.
Considerations for discontinuation of therapy	
In the pivotal BeneGene-2 trial, participants were requested to suspend their FIX prophylaxis regimen after fidanacogene elaparvovec infusion; however, FIX replacement was allowed as needed. The protocol contained guidance for the treating physician on when to consider resuming FIX prophylaxis for a participant if fidanacogene elaparvovec was not efficacious. In this study, this was defined as FIX activity after 12 weeks of ≤ 2% (in the absence of a confirmed FIX inhibitor), as determined by the central laboratory on 2 consecutive samples collected within 2 weeks, and/or 2 or more spontaneous bleeds into a major joint and/or target joint over 4 weeks (in the absence of a confirmed FIX inhibitor) or 3 or more spontaneous bleeds (consisting of joint bleeds and/or significant soft tissue, muscle, or other site bleeds) over 4 weeks (in the absence of a confirmed FIX inhibitor).	This is a comment from the drug plans to inform expert committee deliberations.
The drug plans noted that if treatment failure occurs, the patient may need to restart FIX therapy. How should treatment failure or refractory disease be defined?	The clinical experts consulted by CADTH noted that the determination of treatment failure should be case-by-case, based on the judgment of the treating clinician, although the pivotal trial provided some definitions of treatment failure. The clinical experts consulted by CADTH noted that determining treatment failure is more complicated in clinical practice than in the clinical trial setting. In general, the decision to restart factor concentrate prophylaxis should use the same criteria used for starting prophylaxis in a patient who did not receive gene therapy.

Implementation issues	Response
If fidanacogene elaparvovec fails, can patients be treated with another gene therapy (e.g., a competitor product using a different vector)?	The clinical experts consulted by CADTH noted that if the other gene therapy uses an AAV vector, then the patients may not be eligible to be treated with the other product because anti-AAV nAbs will be positive to the companion test. The clinical experts consulted by CADTH noted that patients may try other products developed based on other viral vectors or even nonviral vectors, although this is hypothetical because currently there is no such gene therapy available.
Considerations for prescribing of therapy	
The drugs plans noted the following considerations for prescribing of therapy: • Fidanacogene elaparvovec is administered as a single-dose IV infusion at 5×10^{11} vg/kg over 60 minutes. • Drug administration requires travel for any eligible residents living in remote regions. • Per the product monograph for fidanacogene elaparvovec, "Treatment must be prescribed and administered in clinical centres by a health professional who is experienced in treating Hemophilia B." • The sponsor notes that patients are anticipated to receive fidanacogene elaparvovec as an outpatient treatment. There is no specific certification of qualification activities required for the centres that will administer fidanacogene elaparvovec. The drug plans note that there will be a limited number of infusion centres.	This is a comment from the drug plans to inform expert committee deliberations.
Does fidanacogene elaparvovec need to be prescribed by or in consultation with specialists who have expertise in the treatment of hemophilia B and/or gene therapy? If so, what specialists need to be involved in the initiation, administration, and follow-up?	The clinical experts consulted by CADTH noted that fidanacogene elaparvovec should be prescribed by or in consultation with specialists who have expertise in the treatment of hemophilia B and/or gene therapy. The clinical experts indicated that fidanacogene elaparvovec should be prescribed based on the judgment of a multidisciplinary team, which is organized by a hemophilia comprehensive treatment centre and may consist of specialists such as a hematologist with experience in treating hemophilia patients, a physiotherapist to assess joint function, a hepatologist for liver related issues, a pharmacist, and an HIV specialist (if the patient is HIV positive).
What would be the most suitable setting for patients to receive the therapy: outpatient clinics at hospitals, specialized medical centres, or hemophilia treatment centres? Does that mean a designated infusion centre? Do the clinical experts anticipate there will be access issues regarding specialists and the infusion centres for patients in some regions?	The clinical experts consulted by CADTH noted that the administration of fidanacogene elaparvovec is on an outpatient basis, and so is follow-up after fidanacogene elaparvovec infusion for most patients (some patients may need to be admitted for follow-up in cases of acute infusion reactions). The clinical experts consulted by CADTH noted that there are hemophilia treatment centres or clinics across Canada, although these centres or clinics may not be evenly distributed within a province. In terms of infusion centres, the clinical experts consulted by CADTH noted that it still remains unclear to them, but presumably there will likely be very few infusion centres across Canada. As a result, the clinical experts consulted by CADTH noted that there will

Implementation issues	Response
	be a potential barrier with respect to the travel and accommodation-related costs associated with patients from remote areas travelling to the infusions centres.
Generalizability	
The inclusion criteria of the pivotal trial stipulated a classification of "moderately severe" or severe, defined by a FIX level of 2% or lower. Could individuals with moderate hemophilia, having levels between 2% and 5%, be considered eligible? Also, would individuals with "mild" hemophilia on regular prophylaxis be included?	The clinical experts noted that the use of a maximum 2% FIX level as the inclusion criterion was chosen by the clinical trialists, but this does not correspond with the conventional definition of hemophilia severity. The clinical experts consulted by CADTH noted that this question is partially overlapped with the previous question regarding how to define moderately severe to severe hemophilia B. The clinical experts consulted by CADTH noted that using FIX level to define eligibility for fidanacogene elaparvovec is not appropriate in clinical practice (although acceptable in clinical trials). Disease severity sufficient to be a candidate for gene therapy should be determined by clinicians based on clinical phenotype. The clinical experts consulted by CADTH noted that patients with moderate hemophilia, having levels between 2% and 5% (or even > 5%), could be eligible for fidanacogene elaparvovec because these patients may have a serious clinical phenotype. The correlation between clinical phenotype and baseline FIX level in hemophilia B can vary. With respect to whether patients with "mild" hemophilia on regular prophylaxis would be eligible for fidanacogene elaparvovec, the clinical experts consulted by CADTH noted that there will be very few patients meeting the description, and these patients with "mild" disease who are on FIX prophylaxis likely require this because they need a high level of protection for their lifestyles (e.g., in the case of competitive or professional athletes). The clinical experts consulted by CADTH noted that this scenario is more of an ethics issue and it remains undecided among them.
The indication restricts treatment to adults aged 18 years and older. Could fidanacogene elaparvovec be used in the pediatric population (aged < 18 years)?	The clinical experts consulted by CADTH noted that fidanacogene elaparvovec should not be given to pediatric patients, given the lack of evidence.
Is there anticipation for any off-label use of the product for patients who do not strictly meet the criteria?	The clinical experts consulted by CADTH noted that there should be no off-label use of fidanacogene elaparvovec based on current evidence.
Do the clinical experts anticipate that there will be an increase in the prescribing of medications outside parameters to prevent inhibitors, to ensure patients maintain the eligibility to use this treatment in the future?	The clinical experts consulted by CADTH noted that this is not expected to be an issue because cases described in the question are very rare and there is currently no such medication that can prevent the development of FIX inhibitors (i.e., nAbs against FIX).
Care provision issues	
Will fidanacogene elaparvovec be supplied directly to infusion clinics from the sponsor, and will there be an additional transportation fee? Are there any different storage conditions, or special equipment required for infusion not normally carried out by the clinic?	The sponsor provided information related to these implementation considerations. Per the sponsor, fidanacogene elaparvovec will be shipped directly from Pfizer's manufacturing and packaging facility to the hospital where the infusion is to occur, and administration will be overseen by the associated hemophilia treatment centre. Fees associated with shipping will be incurred by Pfizer. Fidanacogene elaparvovec will not use specialty pharmacies to manage cold chain

Implementation issues	Response
	supply and infusion. After receiving shipment, the product must be transferred, stored and temperature-monitored in ultra-low temperature environments (i.e., at −90°C to −60°C in a freezer). Original packages removed from frozen storage (−90°C to −60°C) may be kept at room temperature (up to 30°C) for up to 5 minutes for transfer between ultra-low temperature environments. To ensure that gene infusion centres have all necessary processes in place to successfully order, receive, and unpack shipments, as well as return thermal shippers and loggers, Pfizer is offering the option for gene infusion centres to order a dry-run test shipment. Fidanacogene elaparvovec contains genetically modified organisms and has special handling requirements. Recommendations from the safety data sheet, as well as local regulations and practices for the handling of biohazardous agents, must be followed. Personal protective equipment should be worn while preparing or administering fidanacogene elaparvovec. It is advised that all handling and preparations of sterile and cytotoxic or hazardous products must be carried out in Class II of types A2, B1, and B2, and Class III biological safety cabinets, as applicable per local regulations. Gene infusion centres are expected to have all necessary equipment on site required for storage, handling, dose preparation, and administration of fidanacogene elaparvovec. No additional special equipment will be required.
The plans noted the following considerations: • Regular monitoring might be necessary for the management of possible side effects. • Regional expertise may not be readily available should there be any postdischarge complications. This may limit where administration will take place. • During the infusion, patients should be closely monitored for clinical signs and symptoms of infusion reactions and acute or delayed hypersensitivity reactions. During the first 6 months after fidanacogene elaparvovec administration, patients should be monitored for hepatic function (ALT and AST) and factor IX activity levels.	This is a comment from the drug plans to inform expert committee deliberations.
The plans noted the following considerations related to additional supportive medications or other health interventions: • Corticosteroids may be recommended for administration if there is suspicion of immune hepatitis after treatment. • A prophylactic dose of FIX was given before infusion with fidanacogene elaparvovec and, following that, patients discontinued prophylaxis. • In the event of FIX activity decrease, spontaneous bleeds, or surgical procedures after fidanacogene elaparvovec infusion, patients may require administration of additional FIX replacement.	This is a comment from the drug plans to inform expert committee deliberations.

Implementation issues	Response
System and economic issues	
Additional gene therapies for hemophilia B are being reviewed by Health Canada.	This is a comment from the drug plans to inform expert committee deliberations.
There is a high 1-time cost of gene therapy, with unknown additional costs if patients need existing treatment options after gene therapy is administered. The drug plans noted there is uncertainty regarding the duration of efficacy of the gene therapy. The drug plans noted concerns with affordability. The drug plans highlighted the need for a cost comparison between comparator drugs with this product before commencing.	This is a comment from the drug plans to inform expert committee deliberations.
Treatment sites may be limited. What are the parameters of the types of facilities that can manage the therapy, and who should make the determination?	The clinical experts consulted by CADTH noted that the main parameter is the pharmacy's capacity and willingness to store and reconstitute fidanacogene elaparvovec, and this is a primary parameter to determine if fidanacogene elaparvovec can be given or not in a setting. The clinical experts consulted by CADTH noted that the comfort of a hemophilia treatment centre in terms of infusing and dealing with immediate or short-term reactions after infusion of fidanacogene elaparvovec can be a parameter. The clinical experts consulted by CADTH also noted that the requirements in terms of a specific treating room and outpatient medical day unit should not be a major issue.
The drug plans noted a need for long-term follow-up and data collection to assess the efficacy of gene therapy and need for other products. There may be costs associated with data collection and gathering. In addition, they noted a need to monitor access to other therapies after gene therapy is administered.	This is a comment from the drug plans to inform expert committee deliberations.
Given the expected budget impacts and travel that will be required, the drug plans noted a need to consider funding some of these costs, copay assistance, and travel assistance.	This is a comment from the drug plans to inform expert committee deliberations.
There is currently no specific program established for gene therapies. The mechanism of administration and funding are to be determined.	This is a comment from the drug plans to inform expert committee deliberations.

AAV = adeno-associated virus; ALT = alanine transaminase; AST = aspartate aminotransferase; CBS = Canadian Blood Services; FIX = coagulation factor IX; FIX:C = circulating coagulation factor IX; nAb = neutralizing antibody; rFIX = recombinant factor IX; vg = vector genome.

Clinical Evidence

Systematic Review

Description of Study

One phase III, single-arm, open-label clinical trial (the BeneGene-2 trial; N = 45) was included in the systematic literature review conducted by the sponsor. The BeneGene-2 trial was conducted with 45 participants from 27 centres across 13 countries and territories worldwide, including 3 centres in Canada. The BeneGene-2 trial enrolled adult male patients who had moderately severe to severe hemophilia B (defined as FIX:C ≤ 2%). Patients were excluded if their anti-AAVRh74var nAb titre was greater than or equal to 1:1 or if they had a prior history of FIX inhibitors (i.e., nAbs against FIX), or positive FIX inhibitor testing greater than or equal to 0.6 BU.

The primary objective of the BeneGene-2 trial was to determine the noninferiority of fidanacogene elaparvovec relative to the standard of care in Canada, which is FIX prophylaxis, as measured by ABR_{total} at week 12 to month 15 (denoted as year 1) after infusion of fidanacogene elaparvovec. Other efficacy and safety end points were also examined in the BeneGene-2 trial, including the number of patients without bleeds, ABR_{treat}, ABR_{joint}, AIR, annualized FIX consumption, HJHS, Haem-A-QoL, HAL, treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), deaths, withdrawals due to adverse events (AEs), and notable harms (e.g., increased alanine transaminase [ALT], abnormal hepatic function, increased aspartate aminotransferase [AST], increased hepatic enzyme, and increased transaminases). In addition to noninferiority, tests of superiority were also conducted, and a gatekeeping process was applied to control multiplicity of testing multiple end points. For efficacy outcomes such as ABR_{total}, ABR_{treat}, ABR_{joint}, AIR, and annualized FIX consumption, the 45 participants in the pivotal BeneGene-2 trial served as their own controls, using data collected from when these patients were on FIX prophylaxis during an open-label, noninvestigational, prospective, lead-in study (the BeneGene-1 study, N = 102) for comparison.

Patients in the BeneGene-2 trial had a median age of 29 years, ranging from 18 years to 62 years. The majority of patients were white (73.3%), followed by patients identifying as Asian (15.6%), Black or African American (2.2%), American Indian or Alaska Native (0), and Native Hawaiian or other Pacific Islander (0) [all wording for these categories from original source].

The BeneGene-2 trial is ongoing and expected to be completed in December 2029. Data from before the data cut-off date (November 16, 2022) were used to support the sponsor's present submission to CADTH.

Efficacy Results

As of the data cut-off date, the mean (standard deviation [SD]) duration of follow-up in the BeneGene-2 trial was [redacted] with a median (minimum, maximum) of [redacted]. For the lead-in BeneGene-1 study, the mean (SD) duration of follow-up was [redacted] with a median (minimum, maximum) of [redacted].

Bleeding Outcomes

The model estimate of the difference in ABR_{total} between patients treated with fidanacogene elaparvovec during the BeneGene-2 trial versus the same patients treated with routine FIX prophylaxis during the lead-in BeneGene-1 study was −3.13 (95% CI, −5.44 to −0.81) at year 1 after fidanacogene elaparvovec infusion, favouring fidanacogene elaparvovec. The difference in ABR_{total} from week 12 to the data cut-off date (overall) was −3.37 (95% CI, −5.80 to −0.95), in favour of fidanacogene elaparvovec. Overall, 64.4% (29 out of 45) of the patients treated with fidanacogene elaparvovec and 28.9% (13 out of 45) of the patients treated with routine FIX prophylaxis had no untreated or treated bleeds at year 1 after fidanacogene elaparvovec infusion. From week 12 to the data cut-off date after infusion, [redacted] of the patients treated with fidanacogene elaparvovec and [redacted] of the patients treated with routine FIX prophylaxis had no bleeds.

The estimated mean difference in ABR_{treat} between patients treated with fidanacogene elaparvovec during the BeneGene-2 trial and the same patients treated with routine FIX prophylaxis during the lead-in BeneGene-1 study was −2.62 (95% CI, −4.27 to −0.96) at year 1 after fidanacogene elaparvovec infusion and [redacted] from week 12 to the data cut-off date, all favouring fidanacogene elaparvovec. In total, 73.3% (33 out of 45) of the patients treated with fidanacogene elaparvovec and 35.6% (16 out of 45) of the patients treated with routine FIX prophylaxis had no treated bleeds at year 1 after fidanacogene elaparvovec infusion. From week 12 to the data cut-off date after infusion, [redacted] of the patients treated with fidanacogene elaparvovec and [redacted] of the patients treated with routine FIX prophylaxis had no treated bleeds.

The estimated difference in ABR_{joint} between patients treated with fidanacogene elaparvovec and the same patients treated with routine FIX prophylaxis was [redacted] at year 1 after fidanacogene elaparvovec infusion, in favour of fidanacogene elaparvovec. From week 12 to the data cut-off date, the difference was [redacted]. Overall, 68.9% (31 out of 45) of the patients treated with fidanacogene elaparvovec and 44.4% (20 out of 45) of the patients treated with routine FIX prophylaxis had no joint bleeds at year 1 after fidanacogene elaparvovec infusion. From week 12 to the data cut-off date after infusion, [redacted] of the patients treated with fidanacogene elaparvovec infusion and [redacted] of the patients treated with routine FIX prophylaxis had no joint bleeds.

Use of FIX After Infusion of Fidanacogene Elaparvovec

The difference in AIR between patients treated with fidanacogene elaparvovec during the BeneGene-2 trial and the same patients treated with routine FIX prophylaxis during the lead-in BeneGene-1 study was −54.37 (95% CI, −63.64 to −45.10) at year 1 after fidanacogene elaparvovec infusion and [redacted] from week 12 to the data cut-off date, all favouring fidanacogene elaparvovec. From week 12 to the data cut-off date, the difference (95% CI) in the annualized FIX consumption between patients treated with fidanacogene elaparvovec and the same patients treated with routine FIX prophylaxis was [redacted] IU/kg [redacted]), [redacted].

Patient-Reported Outcomes

Among patients treated with fidanacogene elaparvovec, change from baseline at week 52 or week 104 after infusion of fidanacogene elaparvovec [redacted] in the HJHS total score, Haem-A-QoL physical health domain, Haem-A-QoL total score, HAL Complex Lower Extremity Activities score, and HAL total score.

Harms Results

TEAEs were reported in 84.4% (38 out of 45) of the patients in the safety population of the BeneGene-2 trial. The most commonly reported TEAE was increased ALT (26.7%), followed by nasopharyngitis (17.8%) and arthralgia (17.8%). Serious adverse events (SAEs) were reported in 7 patients (15.6%) in the BeneGene-2 trial. The most common SAE was anemia (4.4%). No patients in the BeneGene-2 trial discontinued the study due to AEs or died as of the data cut-off date of November 16, 2022.

In terms of notable harms, increased ALT and abnormal hepatic function occurred in 26.7% (12 out of 45) and 13.3% (6 out of 45) of the patients in the BeneGene-2 trial, respectively. Increased AST, increased hepatic enzyme, and increased transaminases each occurred in 6.7% (3 out of 45) of the patients in the BeneGene-2 trial.

Critical Appraisal

The BeneGene-2 trial, the only eligible study identified from the sponsor-conducted systematic literature review, was a phase III, single-arm, open-label clinical trial that enrolled 45 patients. Although the interpretation of the study results is limited due to the nonrandomized, open-label, single-arm design, the discontinuity design was considered appropriate in the field of hemophilia B by the clinical experts consulted by CADTH for this review. Participants in the BeneGene-2 trial were asked to suspend their FIX prophylaxis regimen after infusion of fidanacogene elaparvovec, but could resume FIX prophylaxis based on the judgment of the investigator and the trial protocol–outlined guidance to the treating physician on when to consider resuming FIX prophylaxis. These conditions in the guidance were considered generally appropriate by the clinical experts consulted by CADTH. Moreover, the resumption of a FIX prophylaxis regimen after infusion in the BeneGene-2 trial was not expected to modify treatment effects, supported by the "jump to reference" sensitivity analysis in which participants who resumed FIX prophylaxis regimens after infusion of fidanacogene elaparvovec were excluded and the difference in ABR_{total} was similar to that of the primary analysis. The patients included in the pivotal BeneGene-2 trial were selected from the lead-in BeneGene-1 study. Out of 102 patients in the BeneGene-1 study, 45 were enrolled in the pivotal BeneGene-2 trial. It was determined by CADTH that the potential selection bias due to a large number of patients being left out was not a serious concern, because the data provided by the sponsor showed that outcomes of the majority of the patients who were left out (i.e., 40 patients were not enrolled in the BeneGene-2 trial because they had not completed the BeneGene-1 study), such as ABR_{total}, ABR_{treat}, and AIR, were similar to the those at year 1 after infusion among the 45 patients enrolled in the BeneGene-2 trial. The documentation of bleeding events in the BeneGene-2 trial relied on the use of an electronic diary by patients, and the determination of whether a bleed needed to be treated relied on a physician's clinical decisions shared with patients. Despite the risk of bias likely being low, CADTH determined, based on information provided by the sponsor, that the potential risk of bias that may lead to exaggeration of treatment effects of fidanacogene elaparvovec (i.e., ABR outcomes) could not be ruled out. Furthermore, due to a lack of comparative data for some end points and the open-label design, reliable assessments of patient-reported outcomes (e.g., HRQoL end points) could not be made. It was determined by CADTH that the gatekeeping process applied to control multiplicity of testing multiple end points was appropriate. However, there were some concerns regarding the assumptions used

in the statistical models in the BeneGene-2 trial, which may make the interpretation of the magnitude of the effect estimates of fidanacogene elaparvovec compared to FIX prophylaxis challenging.

CADTH identified several considerations related to the generalizability of the BeneGene-2 trial. First and most importantly, given the novelty of gene therapy as well as patients' and clinicians' expectations of long-lasting effects, evidence from the current follow-up period ([redacted]) in the BeneGene-2 trial may not be able to be generalized to long-term efficacy and safety. Second, the proposed indication includes patients with "moderately severe to severe" hemophilia B, and defining this has implementation considerations. Whereas the BeneGene-2 trial defined "moderately severe to severe" as FIX:C less than or equal to 2%, the clinical experts consulted by CADTH noted that severity in clinical practice is defined by a patient's phenotype and not simply their factor activity levels. Some patients' disease be considered moderately severe to severe due to clinical symptoms although their FIX level is greater than 2%, according to the clinical experts consulted by CADTH. In addition, the proposed indication does not specify sex, while the BeneGene-2 trial limited enrolment to male patients. However, the clinical experts consulted by CADTH noted that this is not a serious generalizability issue because they did not expect treatment effects to differ by sex, and female patients with moderately severe to severe hemophilia B are very rare. Furthermore, the BeneGene-2 trial only included patients with anti-AAVRh74var nAb titre less than 1:1. According to the clinical experts consulted by CADTH, the efficacy of fidanacogene elaparvovec in patients with anti-AAVRh74var nAb titre greater than or equal to 1:1 remains uncertain. Nonetheless, the clinical experts consulted by CADTH agreed that selection of eligible patients, if fidanacogene elaparvovec were to be publicly reimbursed, should follow the threshold used in the BeneGene-2 study. Lastly, most patients (73.3%) in the BeneGene-2 trial were white, which — according to the clinical experts consulted by CADTH — was a higher proportion than would be expected in the population of patients in Canada.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: ABR_{total}, ABR_{treat}, ABR_{joint}, percentage of patients without bleeds, AIR, annualized FIX consumption, HJHS, Haem-A-QoL (physical health and total scores), HAL (Complex Lower Extremity Activities and total scores), and harms. According to the GRADE guidance, nonrandomized comparative evidence starts at low certainty and noncomparative evidence starts at very low certainty. The GRADE summary of findings is presented in Table 3 and Table 4.

Table 3: Summary of Findings for Fidanacogene Elaparvovec for Patients With Hemophilia B (Outcomes With Comparative Data)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Treated and untreated bleeds				
ABR_{total} Follow-up:	N = 45 (1 single-arm	**Year 1 after infusion of fidanacogene elaparvovec**	Low[a]	Fidanacogene elaparvovec may

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
• Year 1 after infusion of fidanacogene elaparvovec • Overall	study, with intrapatient comparison)	Number (%) of patients without any treated or untreated bleeds: • Fidanacogene elaparvovec: 29 (64.4) • FIX prophylaxis: 13 (28.9) Mean ABR_{total} estimate (95% CI) • Fidanacogene elaparvovec: 1.30 (0.59 to 2.02) • FIX prophylaxis: 4.43 (1.81 to 7.05) Difference in ABR_{total}, negative binomial estimate (95% CI) • −3.13 (−5.44 to −0.81) **Overall** Number (%) of patients without any treated and untreated bleeds: • Fidanacogene elaparvovec: [redacted] • FIX prophylaxis: [redacted] Mean ABR_{total} estimate (95% CI) • Fidanacogene elaparvovec: [redacted] • FIX prophylaxis: [redacted] Difference in ABR_{total}, negative binomial estimate (95% CI) • [redacted]		result in a decrease in annualized bleeding rate for treated and untreated bleeds when compared with FIX prophylaxis.
Treated bleeds				
ABR_{treat} Follow-up: • Year 1 after infusion of fidanacogene elaparvovec • Overall	N = 45 (1 single-arm study, with intrapatient comparison)	**Year 1 after infusion of fidanacogene elaparvovec** Number (%) of patients without any treated bleeds: • Fidanacogene elaparvovec: 33 (73.3) • FIX prophylaxis: 16 (35.6) Mean ABR_{treat} estimate (95% CI) • Fidanacogene elaparvovec: 0.73 (0.25 to 1.21) • FIX prophylaxis: 3.35 (1.71 to 4.98) Difference in ABR_{treat}, negative binomial estimate (95% CI) [redacted] **Overall** Number (%) of patients without any treated bleeds: • Fidanacogene elaparvovec: [redacted] • FIX prophylaxis: [redacted] Mean ABR_{treat} estimate (95% CI)	Low[a]	Fidanacogene elaparvovec may result in a decrease in annualized bleeding rate for treated bleeds when compared with FIX prophylaxis.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Fidanacogene elaparvovec: [redacted] • FIX prophylaxis: [redacted] Difference in ABR_{treat}, negative binomial estimate (95% CI) • [redacted]		
Treated and untreated joint bleeds				
ABR_{joint} Follow-up: • Year 1 after infusion of fidanacogene elaparvovec • Overall	N = 45 (1 single-arm study, with intrapatient comparison)	**Year 1 after infusion of fidanacogene elaparvovec** Number (%) of patients without any treated or untreated joint bleeds: • Fidanacogene elaparvovec: 31 (68.9) • FIX prophylaxis: 20 (44.4) Mean ABR_{joint} estimate (95% CI) • Fidanacogene elaparvovec: [redacted] • FIX prophylaxis: [redacted] Difference in ABR_{joint}, negative binomial estimate (95% CI) [redacted] **Overall** Number (%) of patients without any treated or untreated joint bleeds: • Fidanacogene elaparvovec: [redacted] • FIX prophylaxis: [redacted] Mean ABR_{joint} estimate (95% CI) • Fidanacogene elaparvovec: [redacted] • FIX prophylaxis: [redacted] Difference in ABR_{joint}, negative binomial estimate (95% CI) • [redacted]	Low[a]	Fidanacogene elaparvovec may result in a decrease in annualized bleeding rate for treated and untreated joint bleeds when compared with FIX prophylaxis.
Use of FIX after infusion of fidanacogene elaparvovec				
AIR Follow-up: • Year 1 after infusion of fidanacogene elaparvovec • Overall	N = 45 (1 single-arm study, with intrapatient comparison)	**Year 1 after infusion of fidanacogene elaparvovec** Mean AIR (SD) • Fidanacogene elaparvovec: 4.46 (10.028) • FIX prophylaxis: 58.83 (29.056) Difference in AIR, estimate from paired t test (95% CI) • −54.37 (−63.64 to −45.10) **Overall** Mean AIR (SD) • Fidanacogene elaparvovec: [redacted]	Low[a]	Fidanacogene elaparvovec may result in a decrease in annualized infusion rate when compared with FIX prophylaxis.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• FIX prophylaxis: [redacted] Difference in AIR, estimate from paired t test (95% CI) • [redacted]		
Annualized FIX consumption (IU/kg) Follow-up: • Overall	N = 45 (1 single-arm study, with intrapatient comparison)	**Overall** Mean annualized FIX consumption (SD) • Fidanacogene elaparvovec: [redacted] • FIX prophylaxis: [redacted] Difference in annualized FIX consumption, estimate from paired t test (95% CI) • [redacted]	Low[a]	Fidanacogene elaparvovec may result in a decrease in total FIX consumption when compared with FIX prophylaxis.

ABR_{joint} = annualized bleeding rate for treated and untreated joint bleeds; ABR_{total} = annualized bleeding rate for treated and untreated bleeds; AIR = annualized infusion rate; CI = confidence interval; FIX = coagulation factor IX; SD = standard deviation.

Note: Year 1 referred to the period between week 12 and month 15 after infusion of fidanacogene elaparvovec. Overall referred to the period from week 12 after infusion of fidanacogene elaparvovec to the data cut-off date (November 16, 2022). As of the data cut-off date, the mean (SD) duration of follow-up in the pivotal BeneGene-2 trial was [redacted]) with a median (minimum, maximum) of [redacted]. The baseline for week 52 and week 104 was defined as the last nonmissing measurement before the dosing date (day 1) in the pivotal study. The mean (SD) duration of follow-up in the lead-in BeneGene-1 study was [redacted] with a median (minimum, maximum) of [redacted]

[a]Risk of bias was not rated down. According to the clinical experts consulted by CADTH, although not optimal, the study design adopted by the BeneGene-2 trial was considered to be of sufficiently low risk of confounding and sampling bias to not introduce serious risk of bias. Although there were differences between patients in the proposed indication and patients in pivotal trial (e.g., definition of moderately severe to severe disease, sex of the patients), it was not considered sufficient by the clinical experts consulted by CADTH to result in important differences in the observed effect. Imprecision was not rated down as the improvement was considered clinically meaningful by the clinical experts consulted by CADTH.

Table 4: Summary of Findings for Fidanacogene Elaparvovec for Patients With Hemophilia B (Outcomes without Comparative Data)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Joint health				
HJHS (0 [best] to 124 [worst]) Follow-up: • Week 52 after fidanacogene elaparvovec infusion • Week 104 after fidanacogene elaparvovec infusion	N = [redacted] (week 52) N = [redacted] (week 104) (1 single-arm study)	**Week 52 after fidanacogene elaparvovec infusion** Mean HJHS score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) [redacted] **Week 104 after fidanacogene elaparvovec infusion** Mean HJHS score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) • [redacted]	Very low[a]	The evidence is uncertain about the effect of fidanacogene elaparvovec on HJHS.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
HRQoL				
Haem-A-QoL Physical health domain (5 [best] to 25 [worst]) Total score (0 [best] to 100 [worst]) Follow-up: • Week 52 after fidanacogene elaparvovec infusion • Week 104 after fidanacogene elaparvovec infusion	N = [redacted] (Physical health domain, week 52) N = [redacted] (Physical health domain, week 104) N = [redacted] (Total score, week 52) N = [redacted] (Total score, week 104) (1 single-arm study)	**Physical health domain, week 52 after fidanacogene elaparvovec infusion** Mean Haem-A-QoL physical health score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) [redacted] **Physical health domain, week 104 after fidanacogene elaparvovec infusion** Mean Haem-A-QoL physical health score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) • [redacted] **Total score, week 52 after fidanacogene elaparvovec infusion** Mean Haem-A-QoL total score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) • [redacted] **Total score, week 104 after fidanacogene elaparvovec infusion** Mean Haem-A-QoL total score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) • [redacted]	Very low[b,c,d]	The evidence is uncertain about the effect of fidanacogene elaparvovec on Haem-A-QoL physical health score or total score.
HAL Complex Lower Extremity Activities score (9 [worst] to 54 [best]) Total score (0 [worst] to 100 [best]) Follow-up: • Week 52 after fidanacogene elaparvovec infusion • Week 104 after	N = [redacted] (Complex Lower Extremity Activities score, week 52) N = [redacted] (Complex Lower Extremity Activities, week 104) N = [redacted] (Total score, week 52) N = [redacted] (Total score, week 104) (1 single-arm study)	**Complex Lower Extremity Activities score, week 52 after fidanacogene elaparvovec infusion** Mean HAL Complex Lower Extremity Activities score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) • [redacted] **Complex Lower Extremity Activities Week 104 after fidanacogene elaparvovec infusion** Mean HAL Complex Lower Extremity Activities score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired	Very low[b,e]	The evidence is uncertain about the effect of fidanacogene elaparvovec on HAL Complex Lower Extremity Activities score or total score.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
fidanacogene elaparvovec infusion		t test (95% CI) • [redacted] **Total score, week 52 after fidanacogene elaparvovec infusion** Mean HAL total score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) • [redacted] **Total score, week 104 post fidanacogene elaparvovec infusion** Mean HAL total score (SD) • Fidanacogene elaparvovec: [redacted] Change from baseline, estimate from paired t test (95% CI) • [redacted]		
Harms				
TESAEs Mortality Increased ALT Abnormal hepatic function Increased AST Increased hepatic enzyme Increased transaminases Follow-up: • Overall	N = 45 (1 single-arm study)	TESAEs: 156 per 1,000 (most common: anemia [44 per 1,000]) Mortality: 0 Increased ALT: 267 per 1,000 Abnormal hepatic function: 133 per 1,000 Increased AST: 67 per 1,000 Increased hepatic enzyme: 67 per 1,000 Increased transaminases: 67 per 1,000	Very low[f]	The evidence is uncertain about the effect of fidanacogene elaparvovec on TESAEs, mortality, increased ALT, abnormal hepatic function, increased AST, increased hepatic enzyme, increased transaminases.

ALT = alanine transaminase; AST = aspartate aminotransferase; CI = confidence interval; FIX = coagulation factor IX; Haem-A-QoL = Hemophilia Quality of Life Questionnaire for Adults; HAL = Hemophilia Activities List; HJHS = Hemophilia Joint Health Score; HRQoL = health-related quality of life; MID = minimal important difference; PROBE = Patient Reported Outcomes Burdens and Experiences; SD = standard deviation; TESAE = treatment-emergent serious adverse event.

Note: Year 1 referred to the period between week 12 and month 15 after infusion of fidanacogene elaparvovec. Overall referred to the period from week 12 after infusion of fidanacogene elaparvovec to the data cut-off date (November 16, 2022). As of the data cut-off date, the mean (SD) duration of follow-up in the pivotal BeneGene-2 trial was [redacted] with a median (minimum, maximum) of [redacted] The baseline for week 52 and week 104 was defined as the last nonmissing measurement before the dosing date (day 1) in the pivotal study. The mean (SD) duration of follow-up in the lead-in BeneGene-1 study was [redacted] with a median (minimum, maximum) of [redacted]

[a]In the absence of a comparator arm, certainty of evidence started at very low. Although there were differences between patients in the proposed indication and patients in the pivotal trial (e.g., definition of moderately severe to severe disease, sex of the patients), they were not considered serious enough by the clinical experts consulted by CADTH to result in important differences in the observed effect. There was no MID identified. Imprecision was not rated down, as the improvement was considered clinically meaningful by the clinical experts consulted by CADTH.

[b]In the absence of a comparator arm, certainty of evidence started at very low. This was rated down 1 level for risk of bias due to potential for bias arising from the open-label nature of the study and the subjective nature of the outcome. Indirectness was not rated down. Although PROBE is more commonly used in Canada, this was not considered a serious generalizability issue by the clinical experts consulted by CADTH because all of these HRQoL measurement instruments are closely aligned.

[c]Rated down 1 level for imprecision. The meaningful within-patient change identified in the literature was 10.0 for the Haem-A-QoL physical health domain, [redacted].

[d]Rated down 1 level for imprecision due to the small number of patients involved. The meaningful within-patient change identified in the literature was 7.1 for the Haem-A-QoL total score, [redacted].

[e]Rated down 1 level for imprecision. There was no MID available, and the [redacted].

[f]In the absence of a comparator arm, certainty of evidence started at very low. Although there were differences between patients in the proposed indication and patients in pivotal trial (e.g., definition of moderately severe to severe disease, sex of the patients), they were not considered serious enough by the clinical experts consulted by CADTH to result in important differences in the observed effect. This was rated down 1 level for imprecision due to the small sample size, although the safety profile was considered acceptable by clinical experts consulted by CADTH.

Studies Addressing Gaps in the Evidence From the Systematic Review

The sponsor submitted 2 additional studies to address gaps in the pivotal trial evidence. Study C0371005 was submitted to address a gap in knowledge of the safety and kinetics of fidanacogene elaparvovec. Study C0371003 was a corresponding extension study submitted to address the gap in knowledge of the longer-term efficacy and safety of fidanacogene elaparvovec. Patients who completed Study C0371005 were encouraged to enrol into Study C0371003 to evaluate fidanacogene elaparvovec for up to an additional 5-year longer-term follow-up.

Study C0371005

Description of Study

Study C0371005 (N = 15) was a phase I/IIa, open-label, nonrandomized, dose-escalation, multicentre study. The objective was to evaluate the safety, tolerability, and kinetics of a single IV infusion of fidanacogene elaparvovec (dose of 5×10^{11} vg/kg) in participants with hemophilia B with endogenous FIX levels less than or equal to 2%. Patients were followed for 52 weeks. No formal efficacy evaluations were performed. All efficacy analyses were exploratory in nature. The safety analysis set included 15 participants who received the infusion.

All 15 participants enrolled were male, with a mean age of 38.6 years, ranging from 18 years to 61 years. The majority of participants were white or “Caucasian” (80.0%) [wording from original source]. The majority of participants had no family history of FIX inhibitor (80.0%) and had hemophilia B with a FIX:C level less than 1% (66.7%).

Efficacy Results

Bleeding Outcomes

Among 15 treated participants, 12 participants (80.0%) did not experience any on-study bleeds. No traumatic bleeds were observed during the study, and all 3 participants who experienced bleeding episodes had spontaneous bleeds. The median ABR during the 52-week period preceding fidanacogene elaparvovec infusion (historical) was 4.00, ranging from 0.0 to 48.0. The median ABR decreased to 0.00 (range: 0.0 to 4.0) during the 52-week period following fidanacogene elaparvovec infusion (on study). The mean ABR decreased from 8.87 (SD = 14.040) to 0.40 (SD = 1.060).

The overall mean (SD) annualized FIX production consumption was [redacted] IU in all 15 participants, with a mean (SD) of [redacted] IU in the 11 participants previously on prophylaxis treatment and [redacted] IU in the 4 participants previously on on-demand treatment.

During the 52-week period preceding screening, the mean (SD) number of target joint bleeds was [redacted] in a total of 5 participants (4 participants previously on prophylactic treatment and 1 participant previously on on-demand treatment). The mean (SD) number of target joint bleeds decreased from [redacted] in 4 participants

to [redacted] occurring in 2 participants previously on prophylactic treatment from 52 weeks preceding screening to end of study.

Patient-Reported Outcomes

The assessments of HJHS, HAL, and the McGill pain questionnaire were added in a protocol amendment; therefore, only the final [redacted] participants enrolled were evaluated for these assessments.

Regarding HJHS, [redacted] participants had assessments done at baseline and at the end of the study. In general, a [redacted].

A [redacted] participants who had assessments done at baseline and at the end of the study. A [redacted] was also observed in [redacted], as well as in the [redacted].

Harms Results

Fourteen out of 15 participants (93.3%) reported at least 1 TEAE. A total of 81 TEAEs were reported in the study. The most commonly reported TEAEs were in the system organ class of infections and infestation (8 participants, 53.3%), gastrointestinal disorders (7 participants, 46.7%), and musculoskeletal and connective disorders (6 participants, 40.0%). The majority of TEAEs (53 out of 81, 65.4%) were mild in severity, and the other 28 (34.6%) were moderate in severity. There were no study drug discontinuations, study discontinuations, SAEs, or deaths reported in the study.

Study C0371003

Description of Study

Study C0371003 (N = 17) is a phase IIa, open-label, nonrandomized, longer-term, follow-up study designed to evaluate the safety and efficacy of previously administered fidanacogene elaparvovec at a dose of 5×10^{11} vg/kg for up to 6 years. Participants enrolled in this study either had been dosed with fidanacogene elaparvovec in Study C0371005 (summarized previously; N = 14) or received fidanacogene elaparvovec in a dose-escalation substudy (N = [redacted]) within this study. Results presented in this report are for the cohort of 14 patients from Study C0371005 who entered Study C0371003. The dose-escalation substudy has not been covered in this report due to the small number of participants and because the dose of fidanacogene elaparvovec used did not align with the recommended dose (patients received a dose of [redacted]).

The primary outcome measures for Study C0371003 were related to safety and immunogenicity, while secondary measures were related to efficacy. As the primary objective of this study was safety, no hypothesis testing was planned and all summaries are descriptive.

At the data cut-off date (November 2, 2022), 2 patients had discontinued from the study, 5 participants had completed the longer-term follow-up, and 7 participants are ongoing. The duration of follow-up at data cut-off ranged from [redacted] after fidanacogene elaparvovec infusion.

The mean age of participants was 40.1 years, ranging from 18 years to 61 years at the time of fidanacogene elaparvovec infusion. Most participants were aged 35 years or older (71.4%) and were white (85.7%). There were 10 participants on FIX prophylaxis and 4 participants using on-demand regimens before fidanacogene elaparvovec infusion. All participants had FIX levels less than or equal to 2%.

Efficacy Results

Bleeding Outcomes

Mean ABR_{treat} remained lower than 1.0 from year 2 through year 6 after infusion with [redacted] participants ([redacted]) having no bleeds during their entire time in the study. The mean (SD) treated ABR was [redacted], [redacted], [redacted], [redacted] and [redacted] during years 2, 3, 4, 5, and 6 after infusion, respectively. [redacted] participants had treated bleeds during years 2 through 6.

AIR generally decreased over the entire follow-up periods, from a mean of [redacted] in year 2 to [redacted] in year 6 after fidanacogene elaparvovec infusion. The mean (SD) AIR was [redacted], [redacted], [redacted], [redacted] and [redacted] during years 2, 3, 4, 5, and 6 after infusion, respectively.

As of the data cut-off date, there were no prophylactic infusions in the study, and no participants had resumed prophylaxis. Median total factor consumption and annualized FIX consumption, excluding consumption required for surgery, was [redacted] for year 2 through year 6. [redacted] of the 14 participants have had no nonsurgical FIX consumption over the longer-term follow-up period.

From week 52 to week 130 after fidanacogene elaparvovec infusion, the number of participants with target joint bleeds decreased from [redacted] to [redacted], based on target joint assessment questionnaire results. [redacted] had target joint bleeding reported beyond week 130 as of the data cut-off (from week 156 to week 312 or end of study).

Patient-Reported Outcomes

The HJHS, an exploratory end point, was added after most participants were dosed, resulting in a low number of assessments at baseline. The baseline HJHS score was the last nonmissing measurement before fidanacogene elaparvovec infusion in Study C0371005. The median HJHS total scores were [redacted] at baseline, [redacted] at week 156, [redacted] at week 208, [redacted] at week 260, and [redacted] at week 312 or end of study.

Haem-A-QoL total scores and domain scores [redacted] throughout the longer-term follow-up period (years 2 through 6). Median change from baseline in Haem-A-QoL total scores ranged from [redacted] over longer-term follow-up (years 2 through 6).

Mean HAL domain scores [redacted] and the total score [redacted] at all after fidanacogene elaparvovec infusion visits over the longer-term follow-up period (years 2 through 6). HAL scores can range from 0 to 100, with higher scores indicating fewer functional limitations.

Harms Results

Of the 10 TEAEs reported, 5 were mild, 1 was moderate, and 4 were severe. These 10 TEAEs included 9 SAEs and 1 nonserious AE (back pain). The most frequently reported TEAEs, regardless of severity, were related to musculoskeletal and connective tissue disorders in 2 participants (14.3%).

Four (28.6%) of the 14 participants experienced a total of 9 SAEs. No participants discontinued from the study due to AEs. There were no deaths.

No participants experienced hypersensitivity reactions or another AESI. During the longer-term follow-up period, 8 of 14 participants experienced ALT increase above ULN, 3 of which had AST increase above ULN. None of these cases were managed with corticosteroids and as of the data cut-off, all of these participants had ALT and AST levels back within normal limits except for 1 patient who completed the study with ALT level above ULN. Regarding immunogenicity, all 14 participants remained negative for FIX inhibitor during the study.

Critical Appraisal

Internal Validity

Study C0371005 was an open-label, single-arm, multicentre, phase I to IIa study. All efficacy analyses were exploratory in nature and were presented using descriptive statistics. The absence of a comparator group limited the interpretation of results because causality cannot be established. The open-label design may have biased the reporting of some end points because awareness of the study treatment received may influence the perception of improvement and/or harms by patients and clinicians, particularly for outcomes that are subjective in measurement and interpretation (e.g., patient-reported outcomes, subjective AEs). The follow-up period was only 1 year, making it insufficient to draw any definite conclusions regarding long-term efficacy and safety outcomes. In addition to the general limitations of the study design, the HJHS and HAL assessments were added to the study later, during a protocol amendment; hence, data were missing for most of the participants (only 4 patients contributed data to the analyses). As such, no conclusions can be drawn for these outcomes with certainty.

Study C0371003 provided longer-term follow-up for 14 of the patients previously administered fidanacogene elaparvovec in Study C0371005. The primary objective of Study C0371003 was to evaluate safety, so no hypothesis testing was planned. All efficacy and safety data were summarized descriptively, resulting in no statistical inferences. Data were missing for the assessments of HJHS and HAL in this study as well, for the reasons previously noted for Study C0371005.

In Study C0371003, the duration of follow-up at data cut-off ranged from [redacted] after fidanacogene elaparvovec infusion. Only 5 participants had completed the 6-year longer-term follow-up as of the data cut-off. According to the clinical experts consulted by CADTH, the data provided for up to 6 years of follow-up are limited but reasonable for assessing safety and efficacy in the patient population. The clinical experts consulted by CADTH noted that longer follow-up (for 20 to 25 years) involving more patients is warranted, to make any definite determinations on overall long-term safety and efficacy of fidanacogene elaparvovec. Although Study C0371003 provides the longest-term data available on the efficacy of fidanacogene elaparvovec, this evidence is inconclusive.

External Validity

The external validity was similar to that of the pivotal trial and its corresponding lead-in study. The dose of fidanacogene elaparvovec used in Study C0371005 aligns with the recommended dose in the draft product

monograph. The majority of the patients enrolled were white (80.0% and 85.7% in Study C0371005 and Study C0371003, respectively), which — according to the clinical experts consulted by CADTH — was higher than would be expected in the population of patients in Canada. Both Study C0371005 and Study C0371003 only enrolled male patients, although the clinical experts noted that this is likely not a serious generalizability issue because the treatment effects are not expected to differ by sex due to the same underlying mechanism of disease, and female patients with moderately severe to severe hemophilia B are rare. One of the eligibility criteria in Study C0371005 was hemophilia B with FIX activity of less than or equal to 2% at screening, and historical evidence or being from a documented genotype known to produce a clinically severe phenotype of hemophilia B. The clinical experts consulted by CADTH noted that severity in clinical practice is defined by a patient's phenotype and not simply by their factor activity levels. Some patients' disease could be considered moderately severe to severe due to clinical symptoms although their FIX level is greater than 2%, according to the clinical experts consulted by CADTH. Lastly, generalizability may also be limited by the small sample size.

Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input gathered during this CADTH review, as well as the relevant literature, were reviewed to identify ethical considerations relevant to the use of fidanacogene elaparvovec for the treatment of moderately severe to severe hemophilia B in patients aged 18 years or older.

Ethical considerations identified in this review included those related to the following:

- **Treatment and experiences of hemophilia B:** Ethical considerations highlighted a significant burden associated with the existing standard of care treatment (prophylactic FIX replacement therapy) for people with moderate to severe hemophilia B. Successful treatment with prophylactic FIX replacement therapy requires frequent IV infusions. People experience variable FIX activity levels due to waning of treatment effect, despite high adherence. As a result, they remain susceptible to bleeds and, even when well treated, people with hemophilia B may find it challenging to fully participate in some household, workplace, athletic, or other activities due to the elevated risk of bleeding. As an X-linked condition with infrequent occurrence in females, females with moderate to severe hemophilia B may experience inequitable access to existing care due to misdiagnosis or underdiagnosis.
- **Clinical and economic evidence use in the evaluation of fidanacogene elaparvovec**: Clinical trial evidence indicated treatment with fidanacogene elaparvovec may result in a clinically relevant reduction in the primary end point of annualized bleeding rate of treated and untreated bleeds during the median follow-up period of [redacted]. However, interpretations of the magnitude of treatment effect are deemed uncertain due to the risk of bias in the statistical models used to inform the comparative efficacy of fidanacogene elaparvovec relative to FIX prophylaxis. Similarly, there is also uncertainty regarding the durability of effect and long-term safety. This uncertainty presents challenges for clinical and shared decision-making about the benefits and harms of fidanacogene elaparvovec,

particularly as it is proposed as a 1-time therapy that is meant to remain effective over the duration of one's life. This uncertainty may be further exacerbated for females, who were absent from the trial population, and people of colour, who were underrepresented in the trial. Limited long-term safety and efficacy data also limit the assessment of cost-effectiveness.

- **Clinical use and implementation of fidanacogene elaparvovec as a gene therapy:** The use of fidanacogene elaparvovec as a gene therapy presents some known risks for patients, such as the development of transaminitis, and presently theoretical risks, such as the long-term possibility of genotoxicity leading to the development of cancer. As a result, it is important for clinicians to facilitate robust informed consent and shared decision-making processes with patients, particularly as there is no opportunity to discontinue this 1-time treatment. Further, due to the production of cross-reactive anti-AAV neutralizing antibodies, people may be rendered ineligible for additional gene therapies even if they experience limited-to-no clinical benefit after receiving fidanacogene elaparvovec. Even for those who experience benefits, transgene expression of the AAV vectors used in gene therapies is expected to diminish over time, leading to decreased efficacy and the need to return to FIX prophylaxis. Determining eligibility for fidanacogene elaparvovec may also present ethical challenges, as it is presently unclear who is most likely to benefit from treatment. Furthermore, the absence or underrepresentation of some populations in trials (e.g., females and people of colour) may incidentally lead to inequitable access to treatment if access is prioritized for populations for whom some safety and efficacy data are available. As diagnosis and treatment with fidanacogene elaparvovec necessitate multidisciplinary care in specialized treatment centres, ensuring equitable access to this therapy requires addressing common geographic barriers of access to specialist care and monitoring.
- **Health systems:** Ethical considerations for health systems related to the implementation of fidanacogene elaparvovec highlight the challenges of assessing opportunity costs and making funding and resource allocation decisions for expensive drugs for rare diseases. Given the uncertainty around the durability of effect and safety of fidanacogene elaparvovec, alternative payment models (APMs) have been proposed to help mitigate the risks of paying for a highly expensive gene therapy (with a proposed life-long efficacy) in the absence of long-term data. However, it is important to consider the concomitant challenges of building the data and clinical infrastructure needed to effectively execute the chosen APM. Similarly, it will be important to consider that the design of an APM (e.g., parameters of treatment success) may also impact how the benefits and burdens of risk sharing are distributed between manufacturers, payers, patients, and the public. Clinical experts also noted the potential need to develop clear prioritization criteria should production shortages of the AAV vector used in fidanacogene elaparvovec (AAVrh74) arise. Clinical experts also indicated there may be some geographic challenges to access, as not all treatment centre pharmacies may be able or willing to offer fidanacogene elaparvovec. As a result, some patients may need to travel out of province to access fidanacogene elaparvovec, which can present challenges in determining which jurisdiction(s) are responsible for reimbursing the therapy and other treatment-related costs.

Economic Evidence

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients (aged 18 years and older) with moderately severe to severe hemophilia B
Treatment	Fidanacogene elaparvovec
Dose regimen	Single IV infusion of 5×10^{11} vg/kg of body weight
Submitted price	1×10^{13} vg/mL: $4,773,595.20 per administration
Treatment cost	$4,773,595.20 per administration per patient
Comparators	FIX prophylaxis treatments: • EHL FIX prophylaxis[a] • SHL FIX prophylaxis[b] • SHL/EHL basket of FIX prophylaxis (comprised of 25% SHL and 75% EHL)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (77 years)
Key data sources	Effectiveness of fidanacogene elaparvovec informed by the BeneGene-2 trial; effectiveness of FIX prophylaxis treatments informed by the BeneGene-1study[c]
Key limitations	• The comparative efficacy of fidanacogene elaparvovec is uncertain due to limitations of the evidence comparing fidanacogene elaparvovec to FIX prophylaxis treatments, including the open-label design and self-reported bleeds. • The duration of benefit with fidanacogene elaparvovec is highly uncertain owing to a lack of long-term follow-up data (BeneGene-2 trial: median [redacted] [45 patients]; Study C0371003: median [redacted] [14 patients]). The long-term magnitude of benefit compared to FIX prophylaxis treatments is unknown owing to a lack of comparative data. • Serious AEs were reported in 16% of patients who received fidanacogene elaparvovec in BeneGene-2; however, costs and consequences of AEs were not considered in the sponsor's model. Owing to the lack of a comparator group in BeneGene-2, the relative safety of fidanacogene elaparvovec compared to FIX prophylaxis is unknown. • Patients were assumed to remain in their initial health state for the entire analysis period, which was deemed inappropriate based on clinical expert feedback obtained by CADTH. This feedback indicated that patients with a high number of annual bleeds would undergo additional assessment and individualized treatment and that annual bleeding rates are unlikely to remain static over time. • Administration costs associated with FIX prophylaxis were overestimated. • nAb testing coverage status is uncertain. If costs associated with testing for the presence of nAbs are not covered by the sponsor, costs associated with fidanacogene elaparvovec will be higher than estimated in the sponsor's analysis.
CADTH reanalysis results	• Given the limitations identified within the sponsor's economic analysis, including uncertainty related to the magnitude and duration of benefit for fidanacogene elaparvovec compared to FIX prophylaxis treatments, CADTH was unable to provide a more reliable estimate of the cost-effectiveness of fidanacogene elaparvovec.

Component	Description
	• Based on the sponsor's analysis, fidanacogene elaparvovec was predicted to be more effective (incremental QALYs: 1.08 vs. all comparators) and less costly (incremental costs: $2,871,630 to $5,576,438) compared to FIX prophylaxis. Results were largely driven by the acquisition cost of fidanacogene elaparvovec, as well as the predicted gain in QALYs and cost savings resulting from a reduction in bleeding events, FIX prophylaxis use, and health care resource use. These findings are highly uncertain as most of the incremental QALYs (93%) were accrued on the basis of extrapolation and any predicted cost savings would not be realized until approximately 12 years after fidanacogene elaparvovec infusion. If the magnitude of benefit between fidanacogene elaparvovec and FIX prophylaxis is less than estimated by the sponsor or if actual cost of FIX prophylaxis treatments is lower than incorporated in the sponsor's model, it will take longer for any potential savings to be realized in the health care system.

AE = adverse event; EHL = extended half-life; FIX = factor IX; LY = life-year; nAb = neutralizing antibody; QALY = quality-adjusted life-year; SHL = standard half-life.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients with moderately severe to severe hemophilia B in Canada is uncertain, the uptake of fidanacogene elaparvovec is uncertain and may be underestimated, market share estimates for FIX prophylaxis treatments are not aligned with Canadian clinical practice, the cost of FIX treatments paid by CBS is confidential and uncertain, and it is unclear whether costs associated with testing for nABs will be covered by the sponsor. The CADTH reanalysis was conducted from the perspective of the CADTH participating drug plans. CADTH reanalysis suggests that the reimbursement of fidanacogene elaparvovec for the treatment of moderately severe to severe hemophilia B in patients aged 18 years and older would be associated with a budgetary increase of $127,503,945 over the first 3 years (year 1: $40,579,580; year 2: $58,746,280; year 3: $28,178,085). The estimated budget impact is highly sensitive to the number of patients who receive fidanacogene elaparvovec.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: December 20, 2023

Regrets: None

Conflicts of interest: None

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.