Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

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Draft

Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein (ALTUVIIIO)

Indication: in adults, adolescents and children with hemophilia A (congenital Factor VIII [FVIII] deficiency) for:

- routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- treatment and control of bleeding episodes, or
- perioperative management of bleeding (surgical prophylaxis)

Sponsor: Sanofi-Aventis Canada Inc.

Recommendation: Reimburse with Conditions

Publication Date: April 2025

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.

Recommendation

The CDA-AMC Canadian Plasma Protein Product Expert Committee (CPEC) recommends that ALTUVIIIO be reimbursed for adults and children with hemophilia A (congenital factor VIII [FVIII] deficiency) for: routine prophylaxis to prevent or reduce the frequency of bleeding episodes, treatment and control of bleeding episodes, and perioperative management of bleeding (surgical prophylaxis), only if the conditions in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 phase III, non-randomized, open-label clinical trials (XTEND-1, N = 159 and XTEND-Kids, N = 74) demonstrated that treatment with ALTUVIIIO 50 IU/kg intravenously administered once weekly for 52 weeks resulted in clinical benefit for patients with severe congenital hemophilia A (defined as <1 IU/dL (<1%) endogenous FVIII activity) without FVIII inhibitors. In XTEND-1 and XTEND-Kids, patients who received ALTUVIIIO administered as once weekly prophylaxis for 52 weeks experienced an annual rate of treated bleeds (ABR) that were considered clinically meaningful, with a mean ABR of 0.71 (95% CI, 0.52 to 0.97) and 0.89 (95% CI, 0.56 to 1.42) in the two trials, respectively. The proportion of patients who did not report experiencing a treated bleed was 64.7% and 63.5% in XTEND-1 and XTEND-Kids, respectively. Observations from these trials additionally suggest that the within-group change from baseline to week 52 indicated an improvement in joint health, quality of life, and pain intensity; however, the magnitude of these clinical benefits was uncertain. Indirect evidence submitted by the sponsor suggests that once weekly prophylactic treatment with ALTUVIIIO may be associated with improvement in bleeding outcomes compared with other treatments such as EHL and SHL therapies, or emicizumab, although the magnitude of the clinical benefit of ALTUVIIIO versus these comparator therapies is uncertain and likely overestimated by the study findings. With regards to harms, ALTUVIIIO was well tolerated and no new safety concerns were identified. Further, there were no reports of factor VIII inhibitor development, serious allergic reactions, and thrombotic events.

Patients input received for this review indicated that there is an unmet need for treatment that has higher bleed protection, less pain management, faster recovery from bleeding episodes, and reduced frequency (fewer doses with longer half-life) of treatment. Patients also want treatment that improves their health-related quality of life (HRQoL). Clinician input also indicated that there is an unmet need for patients on other comparator therapies (including emicizumab) who have breakthrough bleeds and for patients who may be at higher risk of bleeding require higher trough factor levels. CPEC concluded that ALTUVIIIO potentially met some of the needs identified by patients. Specifically, it may offer adequate bleed protection at a lower frequency of administration.

The pharmacoeconomic analysis provided by the sponsor was highly uncertain given the evidence base and had methodological concerns. Using the sponsor-submitted price for ALTUVIIIO and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for ALTUVIIIO was approximately $4.4 million per quality-adjusted life-year (QALY) gained compared with SHL agents for prophylaxis in patients with severe congenital hemophilia A. However, when compared to emicizumab and EHL agents, ALTUVIIIO was less costly and more effective. These analyses were based on data from indirect evidence submitted by the sponsor and the XTEND-1 trial. At the ICER including SHL agents, ALTUVIIIO is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for patients with severe congenital hemophilia A. The cost-effectiveness of ALTUVIIIO for routine prophylaxis in patients with mild and moderate hemophilia A, or treatment and control of bleeding episodes, and perioperative management is unknown. Although the budget impact analyses suggest some scenarios of cost savings with ALTUVIIIO with the inclusion of mild-moderate patients and for treatment and control of bleeding episodes, these effects are highly uncertain and overestimated. Given this uncertainty and the unfavorable ICER compared to SHL agents, there is insufficient evidence to support a higher price for ALTUVIIIO compared to current therapies reimbursed for hemophilia A. Due to the lack of direct comparator data demonstrating ALTUVIIIOA superiority over current therapies and uncertainty for the full indication, as well as the existing confidential negotiated price of comparators, a further price reduction may be required to support cost-effectiveness across the full indication. Therefore, the total drug cost of ALTUVIIIO should not exceed the total drug cost of the current therapies reimbursed by the drug programs.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, discontinuation, and prescribing		
1. Eligibility for ALTUVIIIO should be based on the criteria used by Canadian Blood Services for reimbursement of FVIII replacement therapies.	There is insufficient evidence that ALTUVIIIO is clinically superior or inferior to other FVIII replacement therapies currently reimbursed for the management of bleeding in patients with hemophilia A.	Patients with a history of a positive inhibitor test, and patients with a positive inhibitor test result at screening were excluded from the XTEND-1 and XTEND-Kids trials. There is insufficient evidence to support the use of ALTUVIIIO for patients with evidence of FVIII inhibitors. As such, ALTUVIIIO should only be prescribed for patients without active inhibitors.
Pricing		
2. ALTUVIIIO should be negotiated so that it does not exceed the annual drug program cost of treatment currently reimbursed for the prophylaxis of hemophilia A.	The ICER for ALTUVIIIO in the full indicated population is uncertain. The ICER for ALTUVIIIO is approximately $4.4 million per QALY gained when compared with SHL agents (and less costly and more effective than emicizumab and EHL agents), for prophylaxis in patients with severe hemophilia A. However, the comparative clinical and cost-effectiveness of ALTUVIIIO for routine prophylaxis in patients with mild and moderate hemophilia A, or treatment and control of bleeding episodes, and perioperative management is unknown. As such, there is insufficient evidence to justify a cost premium for ALTUVIIIO, for the full indication, over therapies currently reimbursed for the prophylaxis of hemophilia A.	—
Feasibility of adoption		
3. The feasibility of adoption of ALTUVIIIO must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimates.	—

FVIII = Factor VIII; SHL = standard half life; EHL = extended half life; CDA-AMC = Canada drug agency-agence medicament-L'Agence des médicaments du Canada; QALY = Incremental cost-effectiveness ratio; ICER = Incremental cost-effectiveness ratio.

Discussion Points

- **Current treatment options and patient needs**: In Canada, patients with hemophilia A currently have access to recombinant and plasma-derived FVIII replacement therapies (EHL and SHL therapies), all of which are administered by IV two to three times per week, or by once weekly injection for emicizumab. Based on patient input, the pain associated with emicizumab injections may be an issue, and breakthrough bleeds still occur when treated with emicizumab. The clinical experts noted that those who would be best suited for ALTUVIIIO include patients treated with emicizumab who have experienced a sub-optimal response due to breakthrough bleeding events or adverse events like injection pain, or more rarely, those on SHL or EHL FVIII prophylaxis who have challenges with the frequent dosing interval. In addition, the clinical expert noted that patients participating in high-level physical activities may benefit from the sustained high FVIII activity level as well as patients requiring surgery regardless of their current FVIII treatment.

- **Use for the treatment of mild to moderate hemophilia A**: Both the XTEND-1 and XTEND-Kids trials excluded patients with mild to moderate hemophilia A. Increasing evidence in the literature as well as input from the clinical experts suggests that patients with mild to moderate hemophilia A based on factor VIII levels have a risk of bleeding and some will require prophylaxis. It was noted that there are cases where emicizumab, which is reimbursed for patients with severe hemophilia A, may be considered for patients with moderate and more rarely, mild forms of hemophilia A depending on the needs of the individual. Although data on patients with mild or moderate hemophilia A is not available and that generalizability to those patients remains uncertain in both trials, ALTUVIIIO is anticipated to be used in a similar manner to currently reimbursed SHL and EHL therapies. By not restricting reimbursement to patients with severe hemophilia A, individualized treatment decisions can be made under the guidance of a clinician with experience treating patients with hemophilia A to address the morbidity associated with living with hemophilia A.

- **Treatment and control of bleeding episodes (on-demand use), and perioperative use:** Evidence for on-demand use of ALTUVIIIO was very limited by a small sample size (n =26) in the XTEND-1 trial. With on-demand treatment, most patients (96.2%) had an ABR greater than 10, whereas after switching to prophylactic treatment, most patients (76.9%) had no bleeds. Perioperative management of bleeds was also assessed and although the evidence is limited by a small sample size, all surgeries were reported as having a good or excellent hemostatic response to perioperative use of ALTUVIIIO.

- **Study design and limitations:** Both trials were nonrandomized, open-label, multicenter, phase III trials. The clinical experts consulted for this review indicated that alternative designs like single arm trials and intra-patient comparisons are commonly used in hemophilia A to provide a practical evaluation of new therapies and account for the multifactorial nature of bleeding. Based on an intra-patient comparison in arm A of the XTEND-1 trial, ALTUVIIIO result may result in an improved ABR compared to historical prophylaxis (other marketed standard of care FVIII prophylaxis). Although the clinical experts indicated that the reductions in annual bleeding rates were clinically meaningful, CPEC noted that the conclusions about the reductions in bleeding rate relative to any comparator cannot be drawn and the GRADE certainty of evidence is considered low to very low.

- **Comparative evidence:** Direct comparative evidence to other treatments currently reimbursed for the management of hemophilia A was not identified. The sponsor submitted indirect evidence suggested that for patients with severe hemophilia A, prophylactic treatment with ALTUVIIIO was associated with improved bleeding outcomes compared to EHL agents, SHL agents, or emicizumab. However, the magnitude of the clinical benefit of ALTUVIIIO versus these comparator therapies is uncertain and likely overestimated due to the limitations of the available indirect evidence, such as a sizable reduction in the effective sample size after the propensity score weighting analyses, and inadequate or lack of adjustment for potential prognostic factors, which may introduce unmeasurable confounding in the relative treatment effect estimates. The indirect evidence did not include any comparisons for the use of ALTUVIIIO for the treatment and control of bleeding episodes. Due to a lack of direct comparative evidence and the limitations of the indirect evidence, CPEC concluded that the effectiveness of ALTUVIIIO may be comparable to other Factor VIII treatments and emicizumab, and is suitable as another treatment option for individualized treatment of patients with hemophilia A.

- **Interim data from long-term extension of pivotal trials**: The sponsor-submitted interim analysis of the ongoing long-term extension study, XTEND-ed. Outcomes included in the interim analysis include: the occurrence of inhibitor development (primary outcome), annualized bleed rates, treatment of bleeding episodes, safety and tolerability, and peri-operative management.

Evidence for ABR and the results over two additional years of therapy were consistent with what was observed in the pivotal trials. However, the available evidence was only limited to analyses based on conference presentations, which likely impacts the robustness of evidence and conclusions.

- **Challenges in assessing cost-effectiveness for the full indicated population:** The economic evaluation is highly uncertain, only based on indirect comparison with the XTEND-1 trial population (i.e. for prophylaxis in patients with severe congenital hemophilia A) and highly sensitive to the price of comparator therapies. As such no clinical or cost-effectiveness information is available for routine prophylaxis in patients with mild and moderate hemophilia A, or treatment and control of bleeding episodes, and perioperative management across all severities is unknown.
- **Uncertainty in determining the budget impact for the full indicated population:** It is possible that for patients currently opting for ALTUVIIIO for the treatment and control of bleeding episodes (on-demand treatment), the use of ALTUVIIIO may result in budget savings at publicly available list prices. However:
    - the magnitude of clinical benefit of ALTUVIIIO for prophylaxis in patients with severe Hemophilia A is uncertain, likely overestimated, and extrapolated to prophylaxis for patients with mild and moderate Hemophilia A. When considering the budget impact in the population for which the sponsor provided information on cost effectiveness for ALTUVIIIO (i.e., XTEND-1 population, severe Hemophilia A), the analysis continued to estimate overall cost-savings (e.g. a 3-year budget decrease of approximately $8.3 million). However, these savings assumed that the annual bleed rates for severe patients on-demand treatment are approximately double than the rates observed in the on-demand arm or the XTEND-1 trial.
    - in the sponsor submission, patients do not move between treatment types (e.g., on-demand patients cannot switch to receive prophylaxis). Clinical expert opinion suggested that a proportion of patients currently choosing on-demand treatment would opt to switch to prophylaxis if ALTUVIIIO were reimbursed. Therefore, the sponsor submission may overestimate the proportion of patients that would continue to be treated on-demand over time and consequently overestimate the cost-savings from on-demand use.

Background

Hemophilia A is the most common form of hemophilia disease. It is a rare, congenital bleeding disorder caused by mutations in the gene that produces deficiencies in coagulation factors VIII (FVIII), a glycoprotein critical for hemostasis, which leads to excessive bleeding due to the inability to form blood clots. It predominantly affects male patients, although females who are heterozygous carriers can have factor levels in the hemophilic range. In 2023, the Canadian Blood Disorders Registry estimated that there were 3,510 Canadians living with hemophilia A, of whom 1,158 had severe disease. Disease severity is categorized as mild, moderate, or severe and is based on factor activity levels. Normal FVIII activity is considered 40% or higher. Mild hemophilia A is defined by factor levels of 5% to 40% of typical FVIII activity levels, moderate is defined by levels of 1% to 5%, and severe defined by levels less than 1% of typical FVIII activity levels. Patients with hemophilia A experience symptoms such as bleeding into joints, soft tissues and muscles, the mouth, and urine, as well as surface bleeding and easy bruising. Bleeding associated with hemophilia A can result in complications such as joint damage from repetitive bleeding, deep internal bleeding, and neurological problems or death associated with bleeding in the brain. The challenges experienced by patients with hemophilia A can substantially impact patient quality of life and physical, mental, social and educational well-being.

The International World Federation of Hemophilia (WFH) guidelines recommend primary prophylaxis as the standard of care for all patients with severe hemophilia A. The goal of prophylactic therapy is to maintain factor levels above 1% (1 IU/dL) to reduce spontaneous bleeding and better preservation of joint function. Three options for primary prophylaxis treatment exist in the current Canadian landscape: regular intravenous infusion of standard half-life (SHL) FVIII concentrate, regular intravenous infusion of extended half-life (EHL) FVIII concentrate or regular emicizumab subcutaneous injection. Apart from emicizumab which provides a FVIII activity equivalence level of 10-15%, the trough levels of SHL and EHL FVIII concentrates are between 3-5% immediately after infusion. The corresponding suboptimal FVIII levels of these currently available agents results in inadequate bleed protection. Patients with hemophilia A who participate in regular physical activities may time their prophylactic infusion to align with their physical activities or require additional doses on top of their prophylaxis just prior to certain physical activities to mitigate the risk of provoked bleeding.

ALTUVIIIO is approved by Health Canada for the treatment of hemophilia A (congenital FVIII deficiency) in adults, adolescents and children for routine prophylaxis to prevent or reduce the frequency of bleeding episodes, treatment and control of bleeding episodes, and perioperative management of bleeding (surgical prophylaxis). ALTUVIIIO is a recombinant plasma-derived factor VIII product. ALTUVIIIO is available as an intravenous injection and the dosage recommended in the product monograph is as a single dose of 50 IU/kg once weekly for routine prophylaxis. For the treatment and control of bleeding episodes and perioperative management of bleeding, a single dose of 50 IU/kg is recommended and additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered depending on the type of bleeding or surgery.

Sources of Information Used by the Committee

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

- A review of two phase III, open label non-randomized, multicenter studies in adults (at least 12 years of age) and children (less than 12 years) with previously-treated severe hemophilia A without inhibitors; one long-term extension study and one indirect treatment comparison.
- Patients' perspectives gathered by one patient group, the Canadian Hemophilia Society
- Input from public drug plans and Canadian Blood Services that participate in the reimbursement review process
- Two clinical specialists with expertise diagnosing and treating patients with hemophilia A disease
- Input from three clinician groups, Association of Hemophilia Clinic Directors of Canada, Canadian Association of Nurses in Hemophilia Care, and Canadian Physiotherapists in Hemophilia Care
- A review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from clinical expert(s) consulted by for the purpose of this review.

Patient Input

One patient group submission from the Canadian Hemophilia Society (CHS) was received for this review. The CHS is a national voluntary health charity that advocates for improvements in health and quality of life for patients living with inherited bleeding disorders in Canada. Information provided for this submission was gathered through a national online survey distributed both in English and French between April 1, 2024, to June 1, 2024. A total of 104 responses were received. This included 57 patients with severe hemophilia A, 33 with mild hemophilia A, and 14 with moderate hemophilia A. Of these patients, 33 reported a history of FVIII inhibitors.

The patients highlighted joint pain and loss of function, pain from bleeding episodes, invasive medical procedures, surgery complications, restrictions on sport participation, difficulty performing everyday tasks, long recovery times from bleeding episodes as significant symptoms and challenges associated with hemophilia A disease. Respondents also noted the detrimental effects of hemophilia A on their social and psychological well-being.

Overall, 11 patients were on FVIII prophylaxis, 6 were on FVIII for the treatment and control of bleeding episodes while most patients were on emicizumab prophylaxis. Notably, one patient had undergone gene therapy. Overall, most respondents considered their current treatment regimen as 'very effective' or 'quite effective' in stopping/preventing bleeding. Although most respondents indicated that hemophilia A treatment has become simpler, and less burdensome with emicizumab, the pain associated with the injection as a challenge and breakthrough bleeds still do occur. Patients reported that new therapies that can improve hemophilia A disease outcomes such as higher bleed protection, less pain management, reduced frequency (fewer doses with longer half-life) of treatment are needed to improve disease outcomes.

One patient with severe hemophilia A who had received ALTUVIIIO through a special access program reported that since initiating treatment, this patient reported experiencing a sustained high FVIII level, with a factor trough of approximately 15%, that has reduced

their risk of major and subclinical bleeding. Similar effects were reported by other patients, which appear to be maintained even if the injection is up to 2 days late. According to the patient, this has helped reduce the risk of bleeding, and travel has become easier with ALTUVIIIO, due to the more flexible storage requirements compared to previous treatments. The patient reported no disadvantages or side effects of ALTUVIIIO.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review indicated that the most important treatment goals for patients with Hemophilia A are to prevent bleeding, including spontaneous and traumatic bleeding events, to reduce joint pain, to improve health-related quality of life and to achieve unrestricted lifestyle comparable to the general population. The clinical experts noted that the current standard of care for patients with Hemophilia A in Canada is primary prophylactic therapy. The goal of prophylactic treatment is to prevent bleeding, and as newer treatments are available, the overall goal is for patients to attain higher factor levels or near-normal factor levels. According to the clinical experts consulted for this review, there is no current therapy that can modify the underlying disease mechanism of Hemophilia A outside of gene therapy which is currently unavailable in Canada. In addition, apart from emicizumab which provides a steady-state trough level of 10-15%, the trough levels of available SHL and EHL FVIII concentrates are between 3-5% after infusion, with subsequent clearance dependent on the product half-life (but generally 14-18 hours) resulting in less bleed protection. Patients who participate in regular physical activities are at risk of bleeding with present prophylactic regimens. As a result, these patients need additional doses of factor concentrates on top of their regular prophylaxis just prior to certain physical activities to mitigate the risk of provoked bleeding.

According to the clinical experts, ALTUVIIIO will change the treatment landscape for acute bleed and perioperative management, but do not envision ALTUVIIIO to alter the underlying disease process of congenital Hemophilia A. Both clinical experts indicated that ALTUVIIIO will be the first agent in which a period of “normal hemostasis” (FVIII activity greater than 40% for the first four days of treatment) can be achieved without a trade off in burden of treatment. Compared to available treatment options, the clinical experts suggested that ALTUVIIIO would likely be used as a first-line therapy for patients who desire to use FVIII replacement rather than FVIII mimetic therapy or as an alternative or complimentary therapy to emicizumab. If approved as a first-line treatment, there would be no need for SHL FVIII products as the same FVIII levels could be achieved with fewer doses of ALTUVIIIO.

The clinical experts noted that patients on emicizumab who have experienced a sub-optimal response due to breakthrough bleeding events or adverse events like injection pain or more rarely, neutralizing antibodies to emicizumab, those on SHL or EHL FVIII prophylaxis who still struggle with the frequent dosing interval would be best suited for ALTUVIIIO. In addition, patients participating in high-level physical activities may benefit from the sustained high FVIII activity level with improved bleed protection as well as patients requiring surgery regardless of their current FVIII treatment. Conversely, both experts indicated that ALTUVIIIO will not be suitable for patients with FVIII inhibitors.

The clinical experts noted that outcomes used in clinical practice are largely aligned with those used in the pivotal trials, particularly regarding annualized bleeding rate (ABR), which is a common trial endpoint. Other clinical trial outcomes including joint health, quality of life (Haem-A-QoL), and FVIII activity levels, are also closely monitored in clinical practice. Both clinical experts indicated that treatment with ALTUVIIIO will be discontinued if there is evidence of the development of FVIII inhibitors, no evidence of improvement in bleeding episodes, occurrence of adverse events with treatment administration (allergy/anaphylaxis) and loss of intravenous access.

According to the clinical experts, treatment with ALTUVIIIO should be primarily managed within a Hemophilia Treatment Center (HTC), where specialized hematologists and multidisciplinary teams can monitor treatment including pharmacokinetic testing and manage complications, and perioperative or periprocedural guidance.

Clinician Group Input

Three clinician groups: the Association of Hemophilia Clinic Directors of Canada (AHCDC; 5 clinicians contributed to the input), the Canadian Association of Nurses in Hemophilia Care (CANHC; 6 clinicians contributed), and Canadian Physiotherapists in Hemophilia Care (CPHC; 5 clinicians contributed) provided input for this review. AHCDC gathered input through national advisory

boards, expert opinions, and clinical trial experience with ALTUVIIIO. Information from CANHC was provided by members who responded to the call for input while the submission from CPHC was gathered via information from clinician experience, conferences attended and in-services.

Clinician groups noted that the ultimate treatment goal for patients with hemophilia A is to minimize the number of bleeds while slowing hemophilic arthropathy progression. With currently available treatments, achieving this goal requires frequent administration of high treatment doses to overcome short treatment half-lives. This treatment burden is particularly notable in patients who require elevated trough levels due to recent surgical procedures, compromised joint health, or high physical activity levels, according to clinician group input. Consistent with expert input, the clinician groups agreed that current therapies demonstrate variable efficacy.

Aligning with expert input, clinician groups noted that ALTUVIIIO could be used first-line for patients aged two years or older with hemophilia A or offered as an alternative treatment to those receiving other therapies. Patients best suited for treatment with ALTUVIIIO, as identified by clinician groups, were consistent with that of the clinical expert input. Additional patient populations who clinicians noted may benefit from ALTUVIIIO treatment included patients with hemophilic arthropathy or poor venous access. In addition, clinician groups noted that patients with mild hemophilia A receiving therapy for the treatment and control of bleeding episodes and those undergoing surgery or procedures may benefit from ALTUVIIIO. The clinician groups indicated that patients least likely to benefit from ALTUVIIIO are those who are averse to IV infusions, developed FVIII inhibitors, or have achieved zero bleeds on prophylaxis and who feel that switching therapies would have a minimal positive impact on quality of life.

The clinician groups agreed with consulted experts that the outcomes used in the trials to assess response are realistic for clinical practice, adding that patients should be assessed every 6 months to 2 years, depending on disease severity. CANHC noted that a clinically meaningful response to ALTUVIIIO treatment would involve favorable pharmacokinetic profile (improved half-life near normal levels), an absence of FVIII inhibitors, absence of bleeding events, improved stable joint health, improved quality of life and infrequent hospitalizations. The clinician groups' suggested criteria for discontinuation aligned with expert input. AHCDC and CANHC also suggested discontinuation if the patient switches to a non-factor replacement therapy, other experimental therapies, or if the treatment center is unable to perform the required clotting assay. The input received from the clinician group regarding ALTUVIIIO prescribing considerations, including the follow-up of patients by a hemophilia clinic director, was consistent with the clinical expert inputs received for this review.

Drug Program Input

Input was obtained from the drug programs that participate in our reimbursement review process. Please refer to Table 2 for further information. The following were identified as key factors that could potentially impact the implementation of ALTUVIIIO.

- Considerations for initiation of therapy
- Considerations for continuation or renewal of therapy
- Considerations for prescribing of therapy
- Generalizability

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
Are there any special considerations for monitoring response to therapy (e.g., factor levels)?	According to the clinical experts, special considerations for monitoring response to therapy will be an assessment of FVIII levels. The clinical experts recommended one-stage assay as an ideal assessment of FVIII levels to monitor response to therapy as this is reliable compared to chromogenic assay.

Drug program implementation questions	Clinical expert response
	CPEC agreed with the clinical expert and noted that the type of assay should not be deemed a necessary element of prescribing or reimbursement.
Is there any minimum age for treatment eligibility?	The clinical experts noted that there is no minimum age for treatment eligibility when considering initiation of therapy. CPEC agreed with the clinical experts.
If there is treatment failure, is it appropriate for a patient to switch back to comparator therapies, and how long should the interval (wash-out) be before doing so?	The clinical experts indicated that in case of a treatment failure decision making regarding a switch to comparator therapies and the wash out period before initiation on new therapies should be guided by a clinician who has experience treating patients with hemophilia. CPEC agreed with the clinical experts, and also noted that given the large number of comparators and the variability, it would be difficult to establish a generalized “wash-out period”.
The sponsor claims that a significant advantage and safety feature of ALTUVIIIO is its lack of association with the development of factor VIII inhibitors. Only 3.9% of patients in Arm A (5 patients) had a family history of FVIII inhibitors. All patients previously received Factor therapies, so previously untreated patients were not included which are the population at highest risk of developing inhibitors.	According to the clinical experts, clinicians need to continuously assess for the development of inhibitors, especially if ALTUVIIIO is to be used in a previously untreated patient with hemophilia A or initiated in patients with less than 50 exposure days to other FVIII concentrates. CPEC agreed with the clinical experts, but further noted that that treatment selection would be more likely individualized based on other patient needs rather than due a potential lower risk of inhibitor development.
Do patients need to receive another therapy before starting this ALTUVIIIO, and what is the recommended timing between prophylaxis and the infusion of ALTUVIIIO?	The clinical experts indicated that ALTUVIIIO should not be restricted to patients with hemophilia A who have been on a prior therapy. Both clinical experts noted that if a patient is on another therapy, the timing between their prior prophylaxis and initiation of ALTUVIIIO should be based on the half life of prior product, patient characteristics, and FVIII activity levels. CPEC agreed with clinical experts.
Consider alignment with reimbursement criteria for SHL/EHL/emicizumab products.	This is a comment from the drug plans to inform expert committee deliberations.
Considerations for continuation or renewal of therapy	
What objective markers should be used to assess initial and ongoing response to treatment?	The clinical experts consulted for this review noted that the objective markers to consider for continuation or renewal of therapy includes initial and ongoing response to therapy such as assessing ABR, joint health status, frequency and severity of bleeds (including spontaneous, traumatic and target joints), and breakthrough bleeds. CPEC agreed with clinical experts.
Consider alignment with renewal criteria for SHL/EHL/emicizumab products.	This is a comment from the drug plans to inform expert committee deliberations.
Considerations for prescribing of therapy	
Do you anticipate any tailoring therapy (personalizing medical treatment based on individual patient characteristics, such as level of activity, bleeding pattern (minor surgery), presence of inhibitors, etc.)?	The two clinical experts noted they anticipate tailoring of ALTUVIIIO based on pharmacokinetics, and individual patient profile including bleeding pattern, level of physical activity, and joint health status.

Drug program implementation questions	Clinical expert response
	CPEC agreed with clinical experts.
ALTUVIIIO is reported to provide a mean FVIII activity of over 40 IU/dl for most days of the week and 15 IU/dl on day 7. Do you envision any alternate dose or frequency in clinical practice?	According to the clinical experts most patients on ALTUVIIIO would receive the standard dosing of 50 IU/kg once weekly; however, tailoring could be done based on patient physical activity levels, surgeries/procedures, all under the guidance of a clinician with experience treating patients with hemophilia. CPEC agreed with the clinical experts but further noted that although 50 IU/kg once weekly is a typical dose, it should not be the only dosing strategy available. If the appropriate factor levels are not met for clinical need, an additional dose may need to occur within a week, a similar notion to other comparator therapies in bleeding disorders treatment that are guided clinically.
Consider alignment with prescribing criteria for SHL/EHL/emicizumab.	This is a comment from the drug plans to inform expert committee deliberations.
Generalizability	
The pivotal trials only included patients who had previously received treatment with FVIII therapies; would previously untreated individuals (i.e. those who have a risk of Inhibitor development) be eligible for ALTUVIIIO?	The two clinical experts indicated that ALTUVIIIO should not be restricted to persons with hemophilia A who have been on a prior therapy; however, if a previously untreated patient is started on ALTUVIIIO, the clinician should closely monitor for inhibitor formation. CPEC indicated that the inclusion of patients who had received prior treatment with FVIII therapies was to establish a patient population with a baseline disease severity, rather than to suggest that ALTUVIIIO is a “rescue” treatment to be prescribed after other therapies.

FVIII = factor VIII; EHL= extended half-life; ITC = indirect treatment comparison; SHL = standard half-life

Clinical Evidence

Systematic Review

Description of Studies

Two pivotal, phase III open-label, non-randomized, multicenter studies (XTEND-1 and XTEND-Kids) were included in the systematic literature review (SLR) conducted by the sponsor.

A total of 159 patients who were at least 12 years of age with severe hemophilia A without inhibitors were enrolled in the XTEND-1 trial (including 8 Canadian patients from 2 study sites) and divided into two treatment groups: Arm A (N=133) and Arm B (N=26). Patients on a current FVIII prophylaxis treatment regimen and participated in an observational pre-study (242HA201/OBS16221) for at least 6 months prior to baseline of XTEND-1 trial were assigned to Arm A. Those treated with ALTUVIIIO for the treatment and control of bleeding episodes (herein referred to as an “on-demand treatment” regimen) for hemophilia A were assigned to Arm B. Patients in Arm A received a dose of 50 IU/kg once weekly ALTUVIIIO as prophylaxis treatment for 52 weeks and those in Arm B received ALTUVIIIO 50 IU/kg as on-demand treatment of bleeding episodes for the first 26 weeks and then switched to 50 IU/kg weekly prophylaxis treatment regimen with ALTUVIIIO for another 26 weeks. The primary objective of XTEND-1 was to evaluate the efficacy of ALTUVIIIO as a prophylaxis treatment based on the ABR in Arm A (described below). The key secondary endpoint was to evaluate the efficacy of ALTUVIIIO as a prophylaxis treatment based on the intra-patient comparison of ABR during the trial compared to the historical prophylaxis ABR in the 78 patients in Arm A who participated in the observation study

The XTEND-Kids trial included a total of 74 previously treated patients with severe hemophilia A who were less than 12 years old and was comprised of two age cohorts, children less than 6 years (N = 38) and children between 6 to 12 years (N = 36) (including 9

Canadian patients from 4 study sites). All 74 patients received once-weekly IV doses of 50 IU/kg ALTUVIIIO prophylaxis treatment for 52 weeks. The primary objective of XTEND-Kids was to evaluate the safety of ALTUVIIIO in previously treated pediatric patients with severe hemophilia A based on occurrence of inhibitors. The key secondary endpoint was to evaluate the efficacy of ALTUVIIIO as prophylaxis treatment based on ABR, AJBR, joint health and quality of life outcomes.

In both trials, patients with a history of a positive inhibitor test result at screening (defined as ≥0.6 BU/mL at screening), those with serious active bacterial or viral infection within 30 days of screening, history of hypersensitivity or anaphylaxis associated with any FVIII product or had been on emicizumab within the 20 weeks prior to screening were excluded. Both trials evaluated the safety, efficacy, and pharmacokinetics of ALTUVIIIO administered by IV once weekly as prophylaxis or on-demand treatment in previously treated patients with severe hemophilia A without inhibitors.

The objective of both trials was to assess the safety and efficacy of ALTUVIIIO to maintain homeostasis in the following settings: routine prophylaxis, control and prevention of bleeding, and perioperative management, as measured by annualized bleeding rate (ABR), annualized joint bleeding rate (AJBR), intra-patient comparison of ABR (only XTEND-1; participants served as their own controls), development of FVIII inhibitors (only XTEND-Kids) at week 52 following ALTUVIIIO infusion. Other efficacy and safety endpoints in both trials included joint health (Hemophilia joint health score (HJHS), Hemophilia Quality of Life Questionnaire for adults (Haem-A-QoL) and children (Haemo-QoL), withdrawals due to adverse events (AEs); treatment-emergent adverse events (TEAEs); treatment-emergent serious adverse events (TESAEs); deaths; and notable harms. In the XTEND-1 trial, efficacy endpoints were tested hierarchically to maintain the overall Type I error rate of 0.05 or less. All analyses in the XTEND-Kids trial were descriptive in nature and adjustments for multiplicity were not applied.

In the XTEND-1 trial, the mean (SD) age of patients at baseline was 35.4 (15.1) years, ranging from 12 to 72 years, most patients (78.6%) had no family history of FVIII inhibitors. In the 12 months prior to the study, the mean (SD) number of bleeding episodes reported were 3.2 (5.4) in Arm A patients who all previously received a different prophylaxis regimen and 35.7 (22.2) in Arm B patients who previously received on-demand treatment. In the XTEND-Kids trial the mean (SD) age at baseline was 5.99 (2.91) years; ages ranged from 1.4 to 11.0 years, majority (77%) had no family history of FVIII inhibitor and the mean (SD) bleeding episodes in patients on a prophylactic regimen prior to the study was 2.1 (4.2). The XTEND-1 study was completed on 03 February 2022 and the XTEND-Kids trial was completed on 18 January 2023. There were no reported important protocol deviations that could potentially influence the efficacy results in either XTEND-1 or XTEND-Kids.

Efficacy Results

XTEND-1 trial

Bleeding Outcomes

Annualized bleed rate

The primary efficacy endpoint in XTEND-1 was ABR in Arm A (prophylaxis arm) assessed following 52 weeks of ALTUVIIIO for prophylactic use. In the full analysis set (FAS), a total of 86 bleeding episodes were treated with ALTUVIIIO in 133 patients in Arm A during the efficacy period. The median ABR at week 52 was 0.00 (IQR, 0.00 to 1.04), and the mean ABR was 0.71 (95% CI: 0.52 to 0.97). In Arm A, 131 (98.5%) patients had 5 or fewer bleeding episodes per year and 86 (64.7%) patients had no bleeding episodes during the study . Sensitivity analyses were consistent with those of the primary analysis.

Annualized joint bleeding rate

Results for AJBR were consistent with the results for ABR. In Arm A, 37 patients in the FAS had a total of 61 treated joint bleeds. The estimated mean AJBR at week 52 was 0.51 (95% CI: 0.36 to 0.72). Of the 133 patients in Arm A, 131 (98.5%) patients had an AJBR of 5 or fewer episodes per year with 96 (72.2%) patients with no joint bleeds during the study.

In Arm B, estimated mean AJBR at week 52 was 17.48 (95% CI: 14.88 to 20.54). The mean AJBR in Arm B was similar to Arm A after patients had switched to prophylaxis treatment: exposure days 0.62 (95% CI: 0.25 to 1.52). In an intra-patient comparison of AJBR in Arm B, the joint bleeding rate ratio for prophylaxis versus on-demand treatment was 0.04 (95% CI: 0.01 to 0.08).

Intra-patient comparison of ABR

Intra-patient Comparison of ABR between ALTUVIIIO Prophylaxis vs. Historical Prophylaxis

Overall, the number of patients with ABR of 0 who had historical prophylaxis or ALTUVIIIO were 42.3% and 64.1% respectively. In the FAS (N = 78), intra-patient comparison in Arm A showed a mean ABR reduction of 77% (ABR ratio, 0.23; 95% CI = 0.13 to 0.42; p<0.0001) in the efanesoctocog prophylaxis group compared to historical prophylaxis.

For the 26 patients in Arm B, the bleeding rate ratio for prophylaxis versus on-demand treatment was 0.03 (95% CI: 0.02 to 0.07). With on-demand treatment, most patients (96.2%) had an ABR >10, whereas most patients (76.9%) had no bleeds after switching to prophylactic treatment.

Physical Functioning and Pain (QoL)

Haem-A-QoL Physical Health Score and Haemo-QoL Score

In XTEND-1, quality of life data was collected in adult patients ≥17 years of age or older via the Haem-A-QoL Physical Health score and in adolescent patients aged 12 to 16 years via the Haemo-QoL questionnaire. In Arm A, for patients ≥17 years of age (n=98), the estimated mean change from baseline to Week 52 in Haem-A-QoL Physical Health score was –6.74 (95% CI: –10.13 to –3.36; p-value=0.0001). The Haemo-QoL results in the study's adolescent population (all in Arm A) mirrored those of the ≥17 age group, with improvements in Haemo-QoL Physical Health score (mean change from baseline to Week 52 of -2.18, SD = 22.05) and Total Score (–3.45, SD = 8.83), in the 13-to-16-year age group (n = 18). In Arm B, a mean change in Haem-A-QoL Physical Health score of –25.91 (SD = 22.29) by Week 52 was reported. A sensitivity analysis performed for patients ≥17 years of age in Arm A who had rolled over from the OBS16221 study (n=66) also showed an improvement in Haem-A-QoL Physical Health score (LS mean change from baseline to Week 52: –4.04 [95% CI: –8.06 to –0.03]).

PROMIS Pain Intensity and Physical Function

Item 3a of the PROMIS instrument assessed a patient's worst pain in the last 7 days. This item was used to assess pain intensity in the XTEND trials. In Arm A, in participants aged 12 years or older, the estimated mean change from baseline to Week 52 in pain intensity was a difference in score of –0.21 (95% CI: –0.41 to –0.02; p-value=0.0276). In Arm B, the mean change from baseline to Week 52 pain intensity was a difference in score of –0.77 (SD = 0.81).

The PROMIS instrument was also used to assess physical function in adult patients only (at least 18 years of age). In Arm A, of 108 patients, 103 completed the PROMIS-SF Physical Function questionnaire at baseline and 102 at Week 52. The mean change in Physical Health score was 46.80 (SD = 8.82) at baseline to 47.35 (SD = 9.28) with a mean change from baseline to Week 52 of 0.62 (SD = 4.77).

Joint Health

Hemophilia Joint Health Score

In Arm A, the mean HJHS total score at baseline was 18.1 (SD =18.4). The estimated mean change in the HJHS Total score from baseline to Week 52 was –1.54 (95% CI: –2.70 to –0.37; p=0.0101). In Arm B, the mean change from baseline to Week 52 in HJHS total score was –4.1 (SD= 8.7). A sensitivity analysis performed using the data of patients in Arm A who rolled over from the prospective observational OBS16221 study also showed an improvement in HJHS Total score. The LS mean change from baseline to Week 52 was -0.86 (95% CI: -2.38 to 0.66).

Perioperative management outcomes

Number of Injections and Dose to Maintain Hemostasis During Major Surgery

In XTEND-1, 11 out of 12 major surgeries that occurred during the treatment regimen required a single injection of ALTUVIIIO (i.e., the pre-operative loading dose) to maintain hemostasis. The mean (SD) dose per injection was 41.65 (15.21) IU/kg. For 1 surgery, conducted during routine prophylaxis, no pre-operative loading dose was reported on the day before or the day of the surgery.

XTEND-Kids trial

Inhibitor Development to FVIII

Inhibitor Development to FVIII

The primary endpoint of XTEND-Kids was the occurrence of inhibitor development against FVIII based on all patients who had reached at least 50 exposure days. Overall, 65 patients who had reached at least 50 exposure days were analyzed for inhibitors. The incidences of inhibitor development to FVIII were 0.0% (95% CI: 0.0 to 5.5) in patients with ≥50 exposure days to ALTUVIIIO and 0.0% (95% CI: 0.0 to 4.9) in all treated patients.

Bleeding Outcomes

Annualized bleed rate

The overall mean ABR at week 52 was 0.89 (95% CI, 0.56 to 1.42) and a median (IQR) ABR was 0 (0, 1.02). Of the 74 patients, 47 (63.5%) had an ABR of 0, and 25 (33.8%) had an ABR of >0 to 5 at 52 weeks. A total of 64 bleeding episodes were treated with ALTUVIIIO in 27 out of the 74 patients. Results of sensitivity analyses based on mean ABR at 52 weeks on the per protocol set or mean ABR on FAS including patients with data at week 26 were consistent with the primary analysis.

Annualized joint bleeding rate

The overall estimated mean AJBR was 0.59 (95% CI: 0.27 to 1.28), with 0.19 (95% CI: 0.06 to 0.62) in the <6 years of age cohort, and 0.99 (95% CI: 0.38 to 2.60) in the 6 to <12 years of age cohort. Of the 74 patients who were included in the analysis, 61 (82.4%) patients reported no joint bleeds, while 12 (16.2%) patients reported 1 to 5 joint bleeds. One (1.4%) patient had 21 joint bleeds as per analysis, 18 of which were not confirmed by the investigator nor reported by the patient. A sensitivity analysis excluding the participant who did not receive the weekly prophylaxis treatment for an extended period of time showed that the estimated mean AJBR in the 6 to <12 years of age cohort decreased to 0.41 (95% CI: 0.19 to 0.89) and the overall estimated mean AJBR to 0.30 (95% CI: 0.16 to 0.57)

Physical Functioning and Pain (QoL)

Haem-A-QoL Physical Health Score and Haem-A-QoL Score

For patients aged 4 to 7 years, 8 to <12 years, and in respective caregivers, data was collected using 4 separated Haem-A-QoL questionnaires. For patients between the age of 4 and 7, the mean change from baseline to week 52 was –5.31 (SD = 10.83) in the < 6 years of age cohort, and 4.69 (SD = 5.41) in the 6 to <12 years of age cohort. In patients aged 4 to 7 overall, the mean change from baseline to week 52 was –2.46 (SD = 10.49). Parents of children between the age of 4 and 7 were also asked to complete the Haem-A-QoL for a parent-proxy assessment of this outcome. For the overall group, the mean change from baseline based on the parent-proxy was –2.85 (SD = 11.82), which is aligned with the patient-reported results. For patients aged 8 and older, the mean change from baseline to week 52 was –9.79 (SD = 12.18).

PROMIS Pain Intensity and Physical Function

Similar to the XTEND-1 trial, pain intensity was assessed in XTEND-Kids using item a of the PROMIS Pediatric instrument as a change from baseline to week 52. For patients between the age of 5 and 12, a parent or caregiver response was use as a proxy for the child. In the cohort of patients less than 6 years old, the mean change from baseline was –0.44 (SD = 2.65) and for patients between the age of 6 and 12, the mean change from baseline was -0.75 (SD = 2.53). Overall, the mean change in scores form

baseline was –0.62 (SD = 2.52). Patients between the age of 8 and 12 responded to this outcome independently. For patients 8 years of age or older in the 6 to 12 cohort, the mean change from baseline was 0.00 (SD = 2.98).

In the <6 years of age cohort, 8 parents of participants ≥5 years of age completed the PROMIS-SF Physical Function questionnaire at baseline, and 8 parents at Week 52. The mean change from baseline to week 52 in was 3.96 (SD = 6.73, n = 7). In the 6 to <12 years cohort, 14 participants aged ≥8 years completed the PROMIS-SF Physical Function questionnaire at baseline, and 16 participants at week 52. The mean change from baseline to week 52 was 0.78 (SD = 10.48, n = 10). In the 6 to <12 years of age cohort, 16 parents of participants <12 years of age completed the questionnaire at baseline, and 16 parents at week 52. The mean change from baseline to week 52 was -1.36 (SD = 12.15, n = 10).

Joint health

Hemophilia Joint Health Score

In the <6 years of age cohort, 20 patients were aged ≥4 years and the mean change (SD) in HJHS Total score from baseline to Week 52 was 0.2 (8.3). In the 6 to <12 years of age cohort, the mean change (SD) in HJHS Total score from baseline to Week 52 was –1.1 (4.3) in 33 patients.

Perioperative management outcomes

Number of Injections and Dose to Maintain Hemostasis During Major Surgery

In XTEND-Kids, both major surgeries required a single injection of ALTUVIIIO to maintain hemostasis. The mean (SD) dose per injection was 61.13 (1.06) IU/kg.

Harms Results

XTEND-1 trial

Adverse Events

XTEND-1

Of the 159 patients in the Safety Analysis Set (SAS), 123 (77.4%) patients experienced at least 1 TEAE, resulting in a total of 394 TEAEs in the study. The most frequently reported TEAEs greater than 3% of patients were headache (20.1%), arthralgia (16.4%), fall (6.3%), back pain (5.7%), COVID-19 and fatigue (4.4% each), contusion, hemophilic arthropathy, and nasopharyngitis (3.8% each), and joint injury, pain in extremity and toothache (3.1% each). Of the 159 patients, 77 (48.4%) patients had no TEAEs classified as moderate or severe but at least 1 TEAE that was classified as mild. In addition, 39 (24.5%) patients had no TEAEs classified as severe but at least 1 TEAE was classified as moderate, and 7 (4.4%) patients had at least 1 TEAE classified as severe.

XTEND-Kids

Of the 74 patients in the SAS, 62 (83.8%) experienced at least 1 TEAE, resulting in a total of 255 TEAEs. The most frequently reported TEAEs (greater than 5% of patients overall) were SARS-CoV-2 test positive and upper respiratory tract infection (14.9% each), pyrexia (12.2%), asymptomatic COVID-19 (9.5%), gastroenteritis viral, head injury, and nasopharyngitis (8.1% each), arthralgia, pain in extremity, and vomiting (6.8% each), contusion, diarrhea, viral infection, and viral upper respiratory tract infection (5.4% each). The majority of TEAEs were assessed by the Investigator as mild in severity. Of the 74 patients, 43 (58.1%) had at least 1 TEAE of mild intensity and 13 (17.6%) patients had at least 1 TEAE of moderate intensity.

Serious Adverse Events

XTEND-1

A total of 18 TESAEs were experienced in 15 (9.4%) of patients, of which 16 TESAEs were reported in 13 patients in Arm A and 2 TESAEs in 2 patients in Arm B. Hemophilic arthropathy was the most commonly reported SAE, which was reported in 2 (1.3%) patients in Arm A. All other TESAEs were reported in 1 (0.6%) patient each. The majority of TESAEs were assessed by the Investigator as mild to moderate in severity.

XTEND-Kids

A total of 10 TESAEs were experienced in 9 (12.2%) patients. The majority of TESAEs were assessed by the Investigator as mild to moderate in severity. The 5 TESAEs assessed by the Investigator as severe were TESAEs of circumcision and bacteremia, each in 1 patient aged less than 6 years and TESAEs of vascular device occlusion, head injury, and eosinophilic oesophagitis, each in one patient aged 6 to less than 12 years.

Withdrawals Due to Adverse Events

XTEND-1

Two TEAEs in 2 (1.3%) patients resulted in permanent treatment discontinuation. The reason for WDAE was due to d a TESAE of a decrease in CD4 lymphocytes in one patient with a history of HIV infection, and due to a combined tibia-fibula fracture in the other patient who WDAE.

XTEND-Kids

No patients discontinued ALTUVIIIO treatment due to a TEAE during the study.

Mortality

XTEND-1

Death was reported in 1 patient overall who was in Arm B. The patient had a medical history of hepatitis C and died of metastatic pancreatic carcinoma, which was reported as a TESAE. The TESAE was assessed by the Investigator as not related to ALTUVIIIO treatment.

XTEND-Kids

There were no deaths reported during the study.

Adverse Events of Special Interest

XTEND-1

There were no reports of inhibitor development to FVIII nor thromboembolic events during the study.

XTEND-Kids

An event of “hives around eyes, mouth, face, and chest” was reported in a 2-year-old patient after “eating chocolate” was reported in one patient. This patient had no history of allergies at baseline. The event occurred approximately 3 months after the first dose of ALTUVIIIO (weekly prophylaxis) and 3 days after the last injection. There were no reports of thromboembolic events during the study.

Critical Appraisal

The two pivotal trials (XTEND-1 and XTEND-Kids) included in the sponsor’s SLR were phase III, single-arm, open-label clinical trials. Although nonrandomized, open-label, single-arm design limits the interpretation of the efficacy results for both pivotal trials, the clinical experts consulted by CDA-AMC for this review indicated that while traditional RCTs remain the gold standard for many conditions, it is not feasible in Hemophilia A due to ethical constraints, challenges in patient recruitment, and the availability of effective treatments. According to the clinical experts, alternative designs like intra-patient comparisons and historical controls provide practical evaluation of new therapies such as ALTUVIIIO. It was noted that participants in both trials were previously treated patients with severe hemophilia A without inhibitors and in particular, 92 patients (N=82 in Arm A and 10 in Arm B) in the XTEND-1 trial were previously enrolled in a pre-study observational study (242HA201/OBS16221). This was determined by CDA-AMC as a potential selection bias. Additionally, although the sponsor provided data on the baseline characteristics of all participants in the pre-study observational study, the baseline clinical characteristics specific to the patients who continued into XTEND-1 from the observational study were not provided. CDA-AMC notes that this limits the ability to identify pre-existing differences, potentially introducing bias and confounding, although, the clinical experts indicated that the rolled over patients and those in XTEND-1 were likely similar and were not systematically different based on the baseline characteristics for the overall group.

In both trials, bleeding outcomes were measured using ABR and AJBR, both of which are widely accepted endpoints in hemophilia research that provides an objective assessment of bleeding outcomes. Joint health was measured using the HJHS, which is a validated outcome measure but is subject to potential bias particularly due inter-rater variability. Additionally, although the study design was deemed appropriate for data collection across varied populations, the lack of blinding introduces potential bias, as knowledge of treatment assignment may influence reporting on subjective or patient-reported outcomes such as, HRQoL, physical function, and pain outcomes (outcomes related to the Haem-A-QoL and PROMIS instruments). As such, reliable assessments of these outcomes could not be made and there is potential for risk of bias that could lead to the overestimation of the treatment effect of ALTUVIIIO.

Both trials appear to be adequately powered for assessing ABR and joint health outcomes; however, smaller subgroup analyses, such as surgery, perioperative management or specific age groups, may not be fully powered to detect adverse events or efficacy. Both trials included follow-up safety assessments for a few weeks after the last dose, but the duration of the XTEND-1 and XTEND-Kids trials was considered too short to sufficiently evaluate delayed adverse effects and assess the long-term safety of ALTUVIIIO.

While XTEND-1 included a historical control through intra-patient comparison with patients' prior prophylactic regimens in a previous study, this approach lacks randomization, is affected by temporal trend, and is prone to measurement bias, making causal inferences less robust compared to a concurrent randomized control group. Additionally, CDA-AMC notes that the reliance on historical data may introduce variability due to changes in patients' current conditions or other external factors unrelated to treatment efficacy such as carryover effects, making causal inferences less robust. Specifically, the XTEND-1 trial was conducted during the COVID-19 pandemic while the observational pre-study was conducted few years before the pandemic, (patients in these studies were enrolled between 2009 to 2017) , impact from possible change in physical activities related to social distancing which was required on many occasions during pandemic (e.g., intensity, types of physical activities) on the risk of bleeding in patients with hemophilia is uncertain. In both trials, perioperative management outcomes were assessed descriptively based on the rating of hemostatic response on a 4-point ordinal scale performed 24 hours after the surgery by the surgeon or study investigator, as well as the number of injections and mean dose to maintain homeostasis per major surgery. CDA-AMC notes that while this subjective assessment is aligned with how this outcome would be assessed in clinical practice, it is likely subject to bias, especially given that the assessments were performed by those involved in the study.

CDA-AMC identified several considerations related to the generalizability of the XTEND-trials in evaluating the efficacy and safety of ALTUVIIIO. The trials enrolled patients from 6 study sites in Canada and included both adults and children with severe hemophilia A, which enhance the generalizability of the findings. In contrast, the results from the two trials may have limited generalizability as the study population was restricted to patients (without inhibitors) with severe hemophilia A. The clinical experts consulted for this review indicated that there is a subset of patients with mild or moderate hemophilia who may require prophylaxis. The design of XTEND-1 and XTEND-Kids did not include these patients and therefore, the magnitude of the treatment effect in patients with mild and moderate hemophilia A is unclear. According to the clinical experts, the once-weekly dosing of 50 IU/kg used in the trials reflects what is expected in clinical practice. However, specific subgroups, such as patients with obesity or those participating in higher risk physical activity may require adjusted dosing, which was not explored in the trials, and this limits the generalizability of the results to these populations. Although the clinical experts indicated the difficulty in the direct comparison of efanesoctocog with current standard of care, CDA-AMC notes that the lack of direct head-to-head comparison with the current standard of care, such EHL FVIII products or non-factor therapies like emicizumab limits external validity regarding the effectiveness and safety of ALTUVIIIO compared to currently available therapies.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Although GRADE guidance is not available for noncomparative studies, the CDA-AMC review team assessed the two single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a

conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low certainty with no opportunity for rating up.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

Results of GRADE Assessments

Table 3 and Table 4 presents the GRADE summary of findings for ALTUVIIIO from XTEND-1 and XTEND-Kids trials for routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes and perioperative management of bleeding in adults and children with hemophilia A. The selection of outcomes for Grading of GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- ABR
- AJBR
- Intra-patient comparison of ABR
- FVIII inhibitor formation
- HJHS
- Physical functioning and pain outcome (Haem-A-QoL, PROMIS Pain Intensity)
- Perioperative management outcome (mean number of injections to maintain hemostasis during major surgery)
- Harms (TEAE, TESAEs, mortality)

Table 3: Summary of Findings for the Efficacy and Safety of ALTUVIIIO for adults with hemophilia A (XTEND-1)

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
Bleeding outcomes				
ABR, treated bleeding episodes per year Follow-up: 121.2 total patient-years	133 (1 single-arm trial with intra-patient comparison)	ABR (single arm analysis): Number (%) of patients with ABR = 0: 86 (64.7) Mean ABR, model based (95% CI): 0.71 (0.52 to 0.97) ABR (Intra-patient comparison): Mean difference ABR (95% CI): –2.27 (–3.44 to –1.10) Adjusted Mean difference ABR (95% CI): 0.23 (0.13 to 0.42)	Low[b]	ALTUVIIIO may result in an improved ABR compared to historical prophylaxis (other marketed standard of care FVIII prophylaxis) although the evidence is still uncertain.
AJBR, treated joint bleeding episodes per year Follow-up: 121.2 total patient-years	133 (1 single-arm trial)	Number (%) of patients with ABR = 0: 96 (72.2) Mean AJBR, model based (95% CI): 0.51 (0.36 to 0.72)	Very low[c]	The evidence is very uncertain about the effect of ALTUVIIIO on AJBR compared to any comparator.
Joint health				
HJHS, change from baseline in total score (0 [best] to 124 [worst]) Follow-up: 52 weeks	133 (1 single-arm trial)	Mean (SD) change from baseline and week 52: –1.5 (6.4) Mean difference, model based (95% CI): –1.54 (–2.70 to –0.37)	Very low[d]	The evidence is very uncertain about the effect of ALTUVIIIO on HJHS compared to any comparator.
Physical function and pain (QoL)				
Haem-A-QoL, change from baseline in physical health score Total score (0 [best] to 100 [worst])	133 (1 single-arm trial)	Mean (SD) change from baseline and week 52: –6.79 (18.59) Mean difference, model based (95% CI): –6.74 (-10.13 to -3.36)	Very low[d]	The evidence is very uncertain about the effect of ALTUVIIIO on Haem-A-QoL compared to any comparator.

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
Follow-up: 52 weeks				
PROMIS Pain Intensity, change from baseline in worst pain intensity in the past 7 days Scored from 0 (no pain) to 5 (very severe) Follow-up: 52 weeks	133 (1 single-arm trial)	Mean (SD) change from baseline and week 52: –0.21 (1.20) Mean difference, model based (95% CI): –0.21 (–0.41 to –0.02)	Very low[d]	The evidence is very uncertain about the effect of ALTUVIIIO on PROMIS Pain Intensity compared to any comparator.
Perioperative management				
Perioperative management, number of major surgeries with hemostatic response rated as excellent or good by investigator Follow-up: 52 weeks	133 (1 single-arm trial)	Number (%) of major surgeries with hemostatic response rated as excellent or good by investigator: 12 (100)	Very low[e]	The evidence is uncertain about the effect of efanesoctocog for the perioperative management of bleeding in adults with hemophilia A compared to any comparator.
Harms				
TESAEs, n Follow-up: 52 weeks	133 (1 single-arm trial)	Number (%) of patients with ≥1 TESAE: 98 per 1000	Very low[f]	The evidence is very uncertain about the effect of ALTUVIIIO on the risk of TESAE compared to any comparator.

ABR = annualized bleeding rate; AJBR = annualized joint bleeding rate; HJHS = hemophilia Joint health score; SD = standard deviation; CI = confidence interval; Haem-A-QoL = Hemophilia A quality of life questionnaire; PROMIS = Patient-reported outcomes measurement information system; QoL = quality of life; TESAE = treatment emergent serious adverse events; TEAE = treatment emergent adverse events.

Note: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

[a] In absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low for all endpoints. In addition, all outcomes were rated down 1 level for indirectness due to the exclusion of patients with mild or moderate hemophilia A.

[b] Despite the study limitations resulting in the certainty of evidence starting as "very low", the proportion of patients with an ABR of 0 (i.e. no bleeds) reported during the trial, a mean ABR less than 1 that was considered as clinically meaningful by the clinical experts consulted for this review, and an intra-patient comparison suggestive of an improvement in ABR compared to prior historical prophylaxis treatment, the CDA-AMC review team considered the strength of evidence sufficient to rate up one level to "low".

[c] Rated down 1 level for serious study limitations: risk of bias due to the non-randomized study design.

[d] Rated down 1 level for serious study limitations: risk of bias due to the non-randomized, open-label study design.

[e] Rated down 1 level for serious study limitations due to risk bias in measurement of the outcome because of the non-randomized, open-label study design. Rated down 1 level due to imprecision due to insufficient sample size.

[f] Rated down 1 level due to imprecision due to insufficient sample size.

Source: XTEND-1 Clinical Study Report. Details included in the table are from the Sponsor's Summary of Clinical Evidence.

Table 4: Summary of Findings for the Efficacy and Safety of ALTUVIIIO for children with hemophilia A (XTEND-Kids)

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
Inhibitor formation				
FVIII inhibitor formation, occurrence of neutralizing antibodies (inhibitor result of at least 0.6 BU/mL) Follow-up: 52 weeks	74 (1 single-arm trial)	Number of patients with inhibitors: 0 Incidence of inhibitor formation, (95% CI): 0.0 (0.0 to 4.9)	Very low[b]	The evidence is uncertain about the effect of ALTUVIIIO on the development of FVIII inhibitors compared to any comparator.
Bleeding outcomes				
ABR, treated bleeding episodes per year Follow-up: 70.6 patient-years	74 (1 single-arm trial)	Number (%) of patients with ABR = 0: 47 (63.5) Mean ABR, model based (95% CI): 0.89 (0.56 to 1.42)	Very low[c]	The evidence is uncertain about the effect of ALTUVIIIO on ABR compared to any comparator.
AJBR, treated joint bleeding episodes per year Follow-up: 70.6 patient-years	74 (1 single-arm trial)	Number (%) of patients with AJBR = 0: 61 (82.4 Mean AJBR, model based (95% CI): 0.59 (0.27 to 1.28)	Very low[c]	The evidence is very uncertain about the effect of ALTUVIIIO on AJBR compared to any comparator.
Joint health				
HJHS, change from baseline in total score (0 [best] to 124 [worst]) Follow-up: 52 weeks	74 (1 single-arm trial)	Mean (SD) change from baseline and week 52: –0.6 (6.0)	Very low[d]	The evidence is very uncertain about the effect of ALTUVIIIO on HJHS compared to any comparator.
Physical function and pain (QoL)				
Haem-A-QoL, change from baseline in physical health score Total score (0 [best] to 100 [worst]) Follow-up: 52 weeks	74 (1 single-arm trial)	Mean (SD) change from baseline and week 52: • 4 to 7 years (n = 21): –2.46 (10.49) • At least 8 years (n = 14): –9.79 (12.18)	Very low[e]	The evidence is very uncertain about the effect of ALTUVIIIO on Haem-A-QoL compared to any comparator.

Outcome and follow-up	Patients (studies), N	Effect	Certainty[a]	What happens
PROMIS Pediatric Pain Intensity, change from baseline in worst pain intensity in the past 7 days Scored from 0 (no pain) to 10 (worse pain) Follow-up: 52 weeks	74 (1 single-arm trial)	Mean (SD) change from baseline and week 52: • 5 to 12 years, parent-proxy (n = 29): –0.62 (2.52) • 8 to 12 years (n = 14): 0.00 (2.98)	Very low[e]	The evidence is very uncertain about the effect of ALTUVIIIO on PROMIS Pediatric Pain Intensity compared to any comparator.
Perioperative management				
Perioperative management, number of major surgeries with hemostatic response rated as excellent or good by investigator Follow-up: 52 weeks	74 (1 single-arm trial)	Number (%) of major surgeries with hemostatic response rated as excellent or good by investigator: 2 (100)	Very low[f]	The evidence is uncertain about the effect of efanesoctocog for the perioperative management of bleeding in children with hemophilia A compared to any comparator.
Harms				
TESAEs, n Follow-up: 52 weeks	74 (1 single-arm trial)	Number of patients with ≥1 TESAE: 122 per 1000	Very low[g]	The evidence is very uncertain about the effect of ALTUVIIIO on the risk of TESAE outcomes compared to any comparator.

ABR = annualized bleeding rate; AJBR = annualized joint bleeding rate; BU = Bethesda unit; HJHS = hemophilia Joint health score; SD = standard deviation; CI = confidence interval; Haem-A-QoL = Hemophilia A quality of life questionnaire; PROMIS = Patient-reported outcomes measurement information system; QoL = quality of life; TESAE = treatment emergent serious adverse events; TEAE = treatment emergent adverse events.

Note: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

a In absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low for all endpoints. In addition, all outcomes were rated down 1 level for indirectness due to the exclusion of patients with mild or moderate hemophilia A.

b Rated down 1 level for serious study limitations due to risk of bias due to missing data and non-randomized study design. Of note, this outcome was the primary endpoint for XTEND-Kids and assessed as a safety endpoint. It was reported descriptively and not adjusted for multiple comparisons.

c Rated down 1 level for serious study limitations: risk of bias due to the non-randomized study design.

d Rated down 1 level for serious study limitations: risk of bias due to the non-randomized and missing data.

e Rated down 1 level for serious study limitations: risk of bias due to the non-randomized, open-label study design

f Rated down 1 level for serious study limitations due to risk bias in measurement of the outcome because of the non-randomized, open-label study design. Rated down 1 level due to imprecision due to insufficient sample size.

g Rated down 1 level due to imprecision due to insufficient sample size.

Source: XTEND-Kids Clinical Study Report. Details included in the table are from the Sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

One LTE study was submitted for review, XTEND-ed (NCT04644575). The XTEND-ed LTE is an ongoing phase III, open-label, multi-center study to assess long-term safety and efficacy of ALTUVIIIO in previously treated patients with severe hemophilia A. The study began in February 2021 and is estimated for completion in 2027. At the time of this submission, the available evidence was limited to interim analyses based on conference presentations. The submitted interim analyses pertain only to patients rolled over from XTEND-1 and XTEND-Kids into Arm A of the XTEND-ed LTE and reports on efficacy and safety-related outcomes over 2 additional years of treatment with ALTUVIIIO.

Efficacy Results

In the first 2 years of XTEND-ed, the mean overall ABR was 0.72 (SD 1.26) for patients in Arm A of XTEND-1 (prophylaxis arm), 0.42 (SD 0.89) for patients in Arm B of XTEND-1 (on-demand switch to prophylaxis), and 0.70 (SD 1.27) for patients from XTEND-Kids. Mean ABR in XTEND-Kids was also comparable across age groups, between patients <6 years of age (ABR 0.63 [SD 1.18]) and 6-12 years of age (ABR 0.77 [SD 1.37]).

Harms Results

As of the XTEND-ed interim analysis cutoff date, 74% of patients from the XTEND-1 group had at least one TEAE and 12% had at least one serious TEAE. The most common TEAEs (>5% of patients) included COVID-19 (22%), arthralgia (13%), headache (9%), nasopharyngitis (8%), and influenza (6%). Two patients discontinued therapy due to TEAEs.

In the XTEND-Kids group, 61% of patients experienced at least one TEAE and 3% had at least one serious TEAE. The most common TEAEs (>5% of patients) included pyrexia (9%), arthralgia (7%), cough (7%), upper respiratory tract infection (6%), viral upper respiratory tract infection (6%), and oropharyngeal pain (6%). There were no treatment discontinuations in this group due to TEAEs.

As of the XTEND-ed interim analysis cutoff date, there was no development of FVIII inhibitors in either group and no deaths were reported.

Critical Appraisal

The XTEND-ed LTE was designed as an open-label extension to assess long-term efficacy and safety of ALTUVIIIO for the treatment of patients with hemophilia A. This open-label design could bias the magnitude of treatment effect for subjective efficacy outcomes and reporting of safety parameters due to unblinded exposure to the study medication during the treatment period. Statistical hypothesis testing was not part of the design and there was no active comparator or placebo arm. The mean treatment duration in the XTEND-Kids group was less than half of that of the XTEND-1 group, at 36.2 weeks and 82.5 weeks, respectively. Clinical experts noted that while 36 weeks is likely sufficient to assess treatment efficacy, more time is needed to evaluate long-term safety outcomes, such as inhibitor development.

The XTEND-ed Arm A study population for this interim analysis consisted of patients who took part in XTEND-1 and XTEND-Kids, and therefore it is reasonable to expect that the same strengths and limitations related to generalizability apply to the LTE. Given that patients needed to complete XTEND-1 or XTEND-Kids before enrolling, the LTE population is inherently enriched and introduces some selection bias for responders.

Indirect Comparisons

Description of Studies

In the absence of head-to-head evidence comparing ALTUVIIIO to other relevant therapies used to manage hemophilia A, the sponsor submitted 1 ITC report comparing relative treatment effects of ALTUVIIIO versus relevant comparator therapies as prophylactic treatment for adult patients with severe hemophilia A. The ITC report included 2 matching-adjusted indirect comparisons (MAICs) for comparing ALTUVIIIO with a non-factor replacement therapy agent (emicizumab) or an SHL product (octocog alfa), and

1 analysis using propensity score matching (PSM) method for comparing ALTUVIIIO with an EHL agent (efmoroctocog alfa). Outcome measures assessed in this ITC included ABRs for any bleeding, spontaneous bleeding, and joint bleeding.

Efficacy Results

Compared to Emicizumab

Emicizumab Q1W was assessed on 63 patients in arm D of the HAVEN III trial and 119 patients in arm A of the XTEND-1 trial. The estimated effective sample size (ESS) for arm A in XTEND-1 was reduced from 119 to 76 patients following matching, which corresponded to 63.8% of the original sample.

Compared to emicizumab Q1W, treatment with ALTUVIIIO was associated with lower rate of any bleeding (treated and untreated) (IRR [95% CI]: 0.32 [0.19 to 0.56]), treated spontaneous bleeding (IRR [95% CI]: 0.62 [0.25 to 1.50]), and joint treated bleeding (IRR [95% CI]: 0.48 [0.24 to 0.95]).

Compared to Octocog Alfa

Octocog alfa was assessed on 62 patients in arms A and B of the LEOPOLD I trial and 159 patients in pooled arms A and B of the XTEND-1 trial. Baseline characteristics of the XTEND-1 pooled arms were adequately matched to aggregated data from LEOPOLD I arms A and B. The estimated ESS was reduced from 128 to 29 patients following matching, which corresponded to 22.7% of the original sample.

Compared to octocog alfa, treatment with ALTUVIIIO was associated with lower rate of any bleeding (MD [95% CI]: –2.97 [–4.28 to -1.67]), spontaneous bleeding (MD [95% CI]: –2.23 [–3.10 to –1.35]) and joint bleeding (MD [95% CI]: –2.67 [–3.85 to –1.49]).

Compared to Efmoroctocog Alfa

Efmoroctocog alfa was assessed on 117 patients with individualized prophylaxis data in the A-LONG trial and 159 patients in the pooled arms A and B of the XTEND-1 trial. The estimated ESS for XTEND-1 was reduced from 145 to 87 patients following matching which corresponded to 60% of the original sample, and for A-LONG IPD was reduced from 116 to 30 patients following matching which corresponded to 26% of the original sample.

Compared to efmoroctocog alfa, treatment with ALTUVIIIO was associated with lower frequency of any treated bleeding (IRR [95% CI]: 0.29 [0.17 to 0.51]), spontaneous bleeding (IRR [95% CI]: 0.21 [0.09 to 0.49]) and joint bleeding (IRR [95% CI]: 0.37 [0.20 to 0.71]).

Harms Results

Harms outcomes were not assessed in these analyses.

Critical Appraisal

In this ITC, unanchored MAIC or a propensity score matching method was used in balancing the baseline characteristics between the included trials. In the MAICs, these potential effect modifiers or prognostic factors were adjusted for if adequate data was reported in the comparator studies: age, body weight, race, prior treatment regimen, prior frequency of bleeding, presence of targeted joints, comorbidities, and baseline patient-reported outcome values. The clinical experts consulted for this review agreed that these are relevant effect modifiers/prognostic variables and also noted that physical activity level at baseline is an important factor in result interpretation. In addition, the use of historical control for intra-patient comparison of ABR in XTEND-1 may introduce variability due to changes in patients' characteristics or external factors including temporal events unrelated to treatment efficacy. For example, the XTEND-1 trial coincided with the COVID-19 pandemic, where changes in the level of physical activity prior to or during the COVID-19 pandemic may have affected patients' risk of bleeding due to changes in lifestyle and behaviour related to physical activity. As such, there is potential for risk of bias in the included studies due to potential confounding by the heterogeneity in physical activity level at baseline, and the time that patients were treated and evaluated (pre- vs. during pandemic); however, the direction of bias is unclear, and the clinical experts consulted by CDA-AMC did not expect this to significantly impact the results. Furthermore, the clinical experts consulted for this review noted that clinical practice and management of patients with hemophilia A

have evolved considerably in the last 10 years. For example, there has been an increase in the use of factor prophylaxis in patients of all ages and disease severities, factor prophylaxis dosing and frequency are tailored based on patient's own pharmacokinetic profile, bleeding profile, activity levels, and potential impact of a bleeding event. Further, the risk of severe bleeding in patients with factor levels indicative of mild to moderate disease range is recognized and such patients can still benefit from prophylaxis treatment (either factor or non-factor). In addition, many clinicians in Canada have adopted the WFH clinical practice guidelines. All these changes have not been considered in the ITC analyses. Therefore, the study results may be biased.

In the MAIC and PSM analyses, the reduction in ESS after the weighting process ranged from 36% to 77% of the original sample size in the included studies. A significant reduction in sample size can contribute to imprecision and increase uncertainty of the results. A notable reduction in ESS also suggests that the study results may be heavily influenced by a subset of the sample in the trials who may not be representative of the full sample. Harms outcomes, which are important to patients and clinicians, were not assessed in the analyses, representing a gap in evidence.

In the sponsor submitted ITC report, indirect comparisons were conducted to compare ALTUVIIIO (XTEND-1) against emicizumab (HAVEN III), EHL products such as efmoroctocog alfa (A-LONG), and SHL products such as octocog alfa (LEOPOLD I). The clinical experts consulted for this review agreed with the sponsor's assumption that all currently reimbursed drugs in EHL or SHL classes are expected to demonstrate equivalent efficacy within their own classes; therefore, one single drug in the EHL or SHL class can represent all currently available drugs in that particular drug class.

Studies Addressing Gaps in the Evidence From the Systematic Review

No relevant studies addressing gaps in the evidence from the systematic review were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov cohort model
Target population	Adults with hemophilia A (congenital factor VIII deficiency) without inhibitors for routine prophylaxis to reduce the frequency of bleeding episodes. Children were included in a scenario analysis only.
Treatment	ALTUVIIIO (TBC) lyophilized powder for reconstitution 250, 500, 1000, 2000, 3000, and 4000 IU vials
Dose regimen	50 IU/kg IV administered once weekly
Submitted price	ALTUVIIIO 250 IU/vial: $827.50 ALTUVIIIO 500 IU/vial: $1,655 ALTUVIIIO 1000 IU/vial: $3,310 ALTUVIIIO 2000 IU/vial: $6,620 ALTUVIIIO 3000 IU/vial: $9,930 ALTUVIIIO 4000 IU/vial: $13,240 $3.31 per IU for all vials
Submitted treatment cost	$739,164 per year
Comparators	• EHL therapies; represented by Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein (Eloctate) • SHL therapies; represented by Antihemophilic Factor (Recombinant) (Kovaltry) • Emicizumab
Perspective	Canadian publicly funded health care payer

Component	Description
Outcomes	QALYs, LYs
Time horizon	65 years (Lifetime)
Key data sources	• XTEND-1 trial informed the baseline patient population characteristics and the ABR for ALTUVIIIO • Sponsor-submitted ITC (i.e., unanchored MAIC and propensity score analysis) informed ABR for the comparators
Key limitations	• The cost-effectiveness analysis does not accurately represent clinical practice for the entire indicated population. Clinical efficacy was informed by the XTEND-1 trial which recruited patients with severe hemophilia A and, based on an accepted deviation request, the sponsor's only evaluated the prophylaxis use of ALTUVIIIO. The Health Canada indication and reimbursement request is broader as it includes the use of ALTUVIIIO for prophylaxis, treatment or perioperative management of bleeding (hereby referred to as on-demand use for the purpose of this report), without any age or severity restriction. Therefore, the cost-effectiveness of ALTUVIIIO for on-demand use and perioperative management of bleeding and as prophylaxis for mild and moderate patients remains unknown. • Given the limitations with the sponsor's submitted ITCs (e.g., sizable reduction in the effective sample size after propensity score weighting analyses, and inadequate or lack of adjustment for potential prognostic factors which may introduce unmeasurable confounding), the magnitude of clinical benefit of ALTUVIIIO is uncertain and likely to be overestimated. • Within the sponsor's model., the number of bleeds impacts the patients' PS which in in turn determines their quality of life and number of joint replacements needed. The sponsor assumed that higher numbers of joint bleeds would be associated with increases in the PS, despite the lack of evidence establishing the surrogate relationship between AjBRs and PS. The predicted QALY benefits are dependent on the validity of the surrogate relationships between ABRs and joint health (i.e., PS). • Treatment acquisition costs were calculated based on the exact dose required (per mg or per IU). According to the CDA-AMC clinical experts and Canadian Blood Services, patients treated with either ALTUVIIIO, emicizumab or other FVIII comparators would typically have their dose rounded to the nearest whole vial with drug dispensed accordingly to minimize wastage. • Costs of breakthrough bleed were underestimated for SHL and ALTUVIIIO. Clinical expert feedback obtained by CDA-AMC noted that the dose of SHL would be higher than assumed by the sponsor. Costs of breakthrough bleeds in the ALTUVIIIO arm were further not appropriately programed into the model.
CDA-AMC reanalysis results	• The CDA-AMC reanalysis included adjusting the on-demand dosage of SHL to align with clinical practice and correctly programming breakthrough bleeds for ALTUVIIIO. • Deterministic results are presented owing to the limitations with the sponsor's probabilistic analysis. The CDA-AMC reanalysis reported that, in adult patients with severe hemophilia A who require routine prophylaxis, the ICER for ALTUVIIIO was $4,432,402 per QALY gained compared to SHL (incremental costs: $5,502,419; incremental QALYs: 1.25). Emicizumab and EHL remained dominated. At the publicly listed comparator prices, a price reduction of at least 22% is required for ALTUVIIIO (from $3.31 to $2.58 per IU) to be considered cost-effective at a WTP threshold of $50,000 per QALY gained compared to SHL. • A scenario analysis for children with severe hemophilia A estimated similar results (ICER = $4,328,721 per QALY gained compared to SHL). • CDA-AMC was unable to address the limitations associated with the comparative clinical effectiveness, the uncertainties surrounding the association between ABRs joint bleeds and PS, and treatment dispensing. Majority of these issues increase the uncertainty to the modelled clinical benefits. Furthermore, the cost-effectiveness of ALTUVIIIO for on-demand use and perioperative management of bleeding and as prophylaxis for mild and moderate patients remains unknown.

ABR = annualized bleed rate; AjBR = annualized joint bleed rate; EHL = extended half-life; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; MAIC = matching-adjusted indirect comparison; PS = Pattersson score; QALY= quality-adjusted life-year; SHL = standard half-life.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: uncertainty in the cost of comparators due to confidential pricing, uncertainty in the annualized bleed rates (ABR) and drug costs associated with bleeds, uncertainty in the number of Hemophilia patients and their allocation to prophylaxis or on demand treatment depending on severity, wastage was not included in the base case and inappropriately modelled in the submitted scenario analysis, market shares in the reference and new drug scenarios did not align with clinical expectations across treatment paradigms, and uptake of ALTUVIIIO was underestimated for on demand treatment.

The CDA-AMC reanalysis included: capturing breakthrough bleeds for prophylaxis patients; aligning the number of patients with 2023 CBDR report and allocating them across treatment paradigms to align with clinical expectations; updating reference and new scenario market shares; and increasing the uptake of ALTUVIIIO for on demand treatment. Based on the CDA-AMC reanalysis, the budget impact is expected to result in 3-year total cost savings of over $471 million ($87,462,805 in year 1, $158,553,582 in year 2, and $225,455,930 in year 3). Cost-savings were observed in both the prophylaxis ($6,549,544) and on demand setting ($464,922,774). CDA-AMC notes that the cost savings predicted from the model may be overestimated as they rely on prophylaxis bleed rates derived from severe patients for which the magnitude of benefit is highly uncertain and likely overestimated, and on demand bleed rates that may be inflated compared to the available evidence as informed by the on demand arm of the XTEND-1 trial. Given ABR of ALTUVIIIO may be exaggerated across all severities and treatment types, particularly for mild and moderate patients for whom evidence is lacking and for whom the majority of the costs savings are estimated to come from, the budget impact results are highly uncertain.

CDA-AMC conducted several scenario analyses to address the uncertainties in the ABR and the price of the comparator. In a multivariate scenario analysis in which the reimbursement of ALTUVIIIO is aligned with the trial (i.e. reimbursement in severe patients only), bleed rates are decreased by 50% for those treated on demand, and a lower price for emicizumab was assumed (i.e., 90% price reduction as per Hemlibra recommendation), the costs savings predicted from on demand use was no longer offset by the incremental costs expected with prophylaxis use. In such a scenario, the reimbursement of ALTUVIIIO is estimated to result in a 3-year budget impact of approximately $177 million.

CPEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Marissa Laureano, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Andrew Shih, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date:

February 27, 2025

Regrets:

1 expert committee member did not attend.

Conflicts of interest:

None