

Reimbursement Recommendation

Pegunigalsidase Alfa (Elfabrio)

Indication: For the long-term treatment of adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase A)

Sponsor: Chiesi Canada Corp.

Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Elfabrio?

Canada's Drug Agency (CDA-AMC) recommends that Elfabrio should be reimbursed by public drug plans for the treatment of Fabry disease (FD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Elfabrio should only be covered to treat patients based on the criteria used by each of the public drug plans for reimbursement of enzyme replacement therapies (ERTs) (i.e., agalsidase beta and agalsidase alfa) for FD.

What Are the Conditions for Reimbursement?

Elfabrio should only be reimbursed in patients under the care of a clinician experienced in the diagnosis and management of FD and should not be reimbursed when combined with other ERTs or oral chaperone therapy for FD. The total cost of Elfabrio should not exceed the total cost of the least costly comparator treatment for FD.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that treatment with Elfabrio resulted in similar clinical benefits for kidney function, Fabry clinical events, heart complications, and pain compared to agalsidase beta. Indirect comparisons of the results from different studies between Elfabrio and other drugs for FD showed that no treatment was clearly preferred over the others for kidney function, heart complications, and pain outcomes.
- Elfabrio meets some of the needs identified by patients and clinicians, such as having similar effect at slowing disease progression as agalsidase beta, but the long-term effects of Elfabrio and how the drug impacts health-related quality of life (HRQoL) are unknown.
- Based on the CDA-AMC assessment of the health economic evidence, Elfabrio may not represent good value to the health care system at the public list price. The committee determined there is not enough evidence to justify a greater cost for Elfabrio compared with other ERTs or oral chaperone therapy for FD.
- Based on public list prices, Elfabrio is estimated to be associated with budgetary savings to public drug plans of approximately \$2 million over the next 3 years.

Summary

Additional Information

What Is Fabry Disease?

FD is a progressive genetic disorder that can lead to serious organ damage, particularly in the heart, kidneys, and brain. Males tend to have more severe symptoms than females. Patients with classic FD have more severe disease beginning in childhood, whereas nonclassic FD is milder and develops in adulthood. Although there are no known published estimates for how common FD is in the general population, the clinical experts consulted for this review estimated that that prevalence is between 1 in 74,000 to 1 in 50,000 people in Canada has FD.

Unmet Needs in Fabry Disease

Patients need additional treatments that slow disease progression, control symptoms, are less burdensome, and have fewer safety concerns than existing treatments.

How Much Does Elfabrio Cost?

Treatment with Elfabrio is expected to cost approximately \$293,897 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that pegunigalsidase alfa be reimbursed for the long-term treatment of adult patients with a confirmed diagnosis of FD (deficiency of alpha-galactosidase A) only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One double-blind, randomized, noninferiority trial (the BALANCE study; N = 78) in patients aged 18 to 60 years diagnosed with FD, who have reduced kidney function, and at least 1 year of treatment with agalsidase beta, 1 mg/kg every 2 weeks was included in this review. Evidence from the BALANCE study demonstrated that, compared with agalsidase beta, 2 years of treatment with pegunigalsidase alfa, 1.0 mg/kg every 2 weeks, resulted in similar clinical benefit for patients with FD. The between-group treatment difference for estimated glomerular filtration rate (eGFR) slope was -0.36 mL/min/1.73 m² per year (95% confidence interval [CI], -2.44 mL/min/1.73 m² per year to 1.73 mL/min/1.73 m² per year) and pegunigalsidase alfa was considered noninferior to agalsidase beta based on the lower bound of the 95% CI being greater than the noninferiority margin of -3.0 mL/min/1.73 m² per year. According to the clinical experts consulted for this review, results from the BALANCE study suggested that the 2 drugs could be similar for incidence in Fabry clinical events, cardiac complications (based on left ventricular mass index [LVMI]), and pain (as per the Brief Pain Inventory [BPI] Short Form). The sponsor-submitted indirect treatment comparison (ITC) showed that no FD-specific treatment was clearly favoured over another for change in eGFR, LVMI, or BPI score. However, the comparisons were hindered by the significant study and population heterogeneity, unverifiable network meta-analysis (NMA) assumptions, and a high level of uncertainty in the estimates based on very wide credible intervals (CrIs).

Input from patients and clinicians identified a need for additional safe, tolerable, and effective treatments that slow disease progression, control symptoms, are associated with fewer infusion-related reactions (IRRs) and antidrug antibody (ADA) development, and improve HRQoL. CDEC concluded that pegunigalsidase alfa met some of the needs identified by patients, including having similar efficacy and safety as agalsidase beta; however, the impact of pegunigalsidase alfa on HRQoL remains unclear, and the long-term outcomes of this lifelong treatment are still unknown.

At the sponsor-submitted price for pegunigalsidase alfa and publicly listed prices for all other drugs, pegunigalsidase alfa was more costly than agalsidase alfa and less costly than migalastat and agalsidase beta. Because there is insufficient evidence to suggest pegunigalsidase alfa is more effective than its comparators, the total drug cost of pegunigalsidase alfa should not exceed the total drug cost of the least costly treatment for FD.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for pegunigalsidase alfa should be based on the criteria used by each of the public drug plans for reimbursement of ERTs (i.e., agalsidase beta and agalsidase alfa) for FD.	There is insufficient evidence that pegunigalsidase alfa is clinically superior or inferior to agalsidase beta and agalsidase alfa, which are currently reimbursed for FD.	According to the 2020 Canadian Fabry Disease Treatment Guidelines, disease-specific therapy is indicated in patients with a confirmed diagnosis of FD and clinical evidence of organ involvement. Diagnosis involves clinical, biochemical, molecular, and pathologic assessment.
Renewal		
2. Pegunigalsidase alfa should be renewed in a similar manner to ERTs for FD.	There is insufficient evidence that pegunigalsidase alfa should be held to a different standard than ERTs for FD that are currently reimbursed when considering renewal.	According to the 2020 Canadian Fabry Disease Treatment Guidelines, assessment of treatment response for patients newly started on therapy should be conducted every 3 to 6 months for the first 5 years of therapy and then annually thereafter if the patient's condition is stable.
Discontinuation		
3. Pegunigalsidase alfa should be discontinued in a similar manner to ERTs for FD.	When considering discontinuation, there is insufficient evidence that pegunigalsidase alfa should be held to a different standard than ERTs for FD that are currently reimbursed.	According to the 2020 Canadian Fabry Disease Treatment Guidelines, discontinuation of disease-specific therapy should be considered upon occurrence of any of the following: lack of response to treatment after at least 1 year of stable treatment, when life expectancy is estimated to be less than 1 year, permanent and severe neurocognitive decline, severe reduction in HRQoL and functional status, persistent and severe IRRs (despite prophylaxis) or persistent IgE ADAs, lack of response to therapy of organ involvement that initially mandated treatment start, and poor adherence.
Prescribing		
4. Patients must be under the care of a clinician experienced in the diagnosis and management of FD.	This is meant to ensure that pegunigalsidase alfa is prescribed for patients for whom it is appropriate and that adverse effects are managed in an optimized and timely manner.	—
5. Pegunigalsidase alfa should not be reimbursed when combined with other ERTs or oral chaperone therapy for FD.	There is no evidence to support the use of pegunigalsidase alfa in combination with other ERTs or oral chaperone therapy for FD.	—
Pricing		
6. The total cost of pegunigalsidase alfa should be negotiated so that it does not exceed the total	The CDA-AMC clinical review concluded that pegunigalsidase alfa may be similar to agalsidase beta drugs across some	—

Reimbursement condition	Reason	Implementation guidance
drug cost of the least costly comparator treatment for FD.	outcomes. However, the evidence was highly uncertain. The results of the sponsor's submitted NMA are highly uncertain owing to various limitations in the analysis. As a result, CDA-AMC was unable to conclude whether pegunigalsidase alfa was clinically similar to agalsidase alfa and migalastat. As such, there is insufficient evidence to justify a cost premium for pegunigalsidase alfa over the least costly comparator treatment reimbursed for FD.	

ADA = antidrug antibody; CDA-AMC = Canada's Drug Agency; ERT = enzyme replacement therapy; FD = Fabry disease; HRQoL = health-related quality of life; IRR = infusion-related reaction; NMA = network meta-analysis.

Discussion Points

- Unmet needs:** CDEC discussed the unmet needs identified from the patient input, including additional treatments that slow disease progression, control symptoms, are less burdensome, and have fewer safety concerns (specifically IRRs and ADAs). The committee noted that although results from the BALANCE study indicate similar clinical benefit between pegunigalsidase alfa and agalsidase beta, pegunigalsidase alfa does not appear to be less burdensome to patients because both are IV infusions given every 2 weeks. For safety concerns, the committee discussed how pegunigalsidase alfa may result in an increase in severe or very severe IRRs and likely results in a reduction in the incidence of neutralizing ADAs compared to agalsidase beta. However, CDEC noted that the small study population, the limitations in generalizing these findings to real-world clinical practice, and the absence of established minimal important differences prevent firm conclusions from being drawn regarding differences in IRRs and ADAs between pegunigalsidase alfa and agalsidase beta. Additionally, there is a lack of evidence from the BALANCE study on the impact of pegunigalsidase alfa on HRQoL.
- Certainty of evidence:** CDEC noted that despite the very low certainty evidence supporting the efficacy outcomes, the results of the BALANCE study indicate that pegunigalsidase alfa could have a similar effect to agalsidase beta on Fabry clinical events, eGFR slope, LVMI, and pain. The committee discussed the factors that contributed to the reduced certainty of the evidence, including the large noninferiority margin for eGFR slope, lack of noninferiority margins or validated minimal important differences for other clinical outcomes of interest (i.e., Fabry clinical events, LVMI, and pain scores), increased risk of bias in the results, and limitations with generalizability. CDEC also discussed how FD is a rare disease, which may have contributed to the small patient populations in the pegunigalsidase alfa studies and increased uncertainty in the evidence.
- Comparative evidence:** CDEC noted that based on the evidence from the sponsor-submitted ITC, no FD-specific treatment was clearly favoured over another for change in eGFR, LVMI, or the BPI

score. The committee discussed the limitations with the indirect evidence, including the significant study and population heterogeneity, unverifiable NMA assumptions, and high level of uncertainty in the estimates based on very wide CIs.

- **Role of biosimilars:** CDEC considered the potential for biosimilar ERTs to enter the market in the future. At the time of this review no biosimilars were available, thus the comparative efficacy and cost-effectiveness of pegunigalsidase alfa relative to biosimilars of agalsidase alfa or agalsidase beta are unknown. CDEC considered that should a biosimilar of agalsidase alfa or agalsidase beta become available to treat FD, there is the potential that pegunigalsidase alfa might not be cost-effective compared to these biosimilars.

Background

FD is a rare, progressive, X-linked, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A due to a *GLA* variant. This deficiency leads to the progressive accumulation of glycolipids (primarily globotriaosylceramide [Gb3] and globotriaosylsphingosine [lyso-Gb3]) resulting in metabolic dysfunction, cellular death, and eventually, progressive vital organ disease. FD is characterized by development of hypertrophic cardiomyopathy, nephropathy with chronic renal failure, and stroke, and these contribute to reduced HRQoL. Hemizygous individuals (i.e., males) tend to have a more severe phenotype, while heterozygous individuals (i.e., females) tend to have a milder phenotype. Patients with classic FD experience more severe disease with early signs and symptoms manifesting during childhood and adolescence while patients with nonclassic FD typically have milder disease and delayed onset of clinical manifestations with symptoms emerging between 30 and 70 years. Between the sexes, the frequency of FD has been estimated in 1 study to be 1 in 40,000 in males and 1 in 117,000 in females. Published estimates on prevalence and incidence of FD in Canada were not available, but the clinical experts consulted for this review estimated prevalence to be between 1 in 74,000 and 1 in 50,000 in Canada. The testing requirements to confirm a diagnosis of FD are well-established in Canada as outlined in the Canadian Fabry Disease Treatment Guidelines and involve the synthesis of clinical, biochemical, molecular, and pathologic criteria.

According to the clinical experts consulted for this review, the goals of treatment are to delay heart failure, slow decline in kidney function, prevent stroke and transient ischemic attack (TIA), control pain and gastrointestinal symptoms, and improve HRQoL. The 2 types of disease-specific treatments for FD include ERT and pharmacologic chaperone therapy; however, neither of these is completely effective. Patients who have an indication for disease-specific therapy can receive ERT, regardless of the genetic variant, whereas migalastat is indicated only for patients with an amenable genetic variant (found in an estimated 35% of the patients with FD in Canada). Identifying amenability to migalastat has been the main factor influencing the decision between treatment with an ERT and chaperone therapy. Other considerations include the method of administration, disease severity, and the potential for developing ADAs with ERT. Patients with FD may also be treated with nonspecific therapies to address pain and renal, cardiac, neurologic, or gastrointestinal disease.

Pegunigalsidase alfa is an ERT has been approved by Health Canada for the long-term treatment of adult patients with a confirmed diagnosis of FD (deficiency of alpha-galactosidase A). Pegunigalsidase alfa is a pegylated recombinant ERT. It is available as a 2 mg/mL concentrate solution for IV infusion. The dosage recommended in the product monograph is based on body weight at 1 mg/kg administered by IV every other week.

Sources of Information Used by the Committee

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

- a review of 1 phase III, double-blind, noninferiority, randomized controlled trial (RCT) in adult patients with FD who were previously treated with agalsidase beta; 1 open-label extension (OLE) study; 1 ITC; and 1 phase III, open-label, switch-over study to address gaps in the evidence
- patients' perspectives gathered by 1 patient group, the Canadian Fabry Association, along with individual patient testimonials
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with FD
- input from 1 clinician group, the Canadian Fabry Disease Initiative (CFDI)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

CDA-AMC received submissions from 1 patient group, the Canadian Fabry Association, and individual patients. Patient feedback was collected through 3 individual testimonials and semistructured interviews to learn about patients' lived experience. During the interviews, patients reported positive impacts of these treatments. Patients described having more energy, fewer episodes of pain crisis, less gastrointestinal pain, and an ability to carry out everyday life activities. Overall, patients reported a reduction in their overall symptoms and stabilization of cardiac and renal disease.

Patients reported concerns about receiving ERT, including IRRs, and about adverse events such as nausea, fatigue, chills, and fever, as well as consequences of ADAs. According to the Canadian Fabry Association, important outcomes are less frequent infusions, improvement in IRRs, slowed disease progression, as well as prolonged and consistent symptom control.

Patients described the main unmet need as having additional treatments that slow disease progression, control symptoms, and are tolerable. Specifically, for ERT, there is a need for drugs that are associated with fewer IRRs and have less risk of developing ADAs. Patients stated that while there is no cure for FD, they felt that pegunigalsidase alfa could improve patients' HRQoL and health outcomes.

Clinician Input

Input From Clinical Experts Consulted for This Review

According to the clinical experts, although there are disease-specific treatments available for FD, not all patients experience a satisfactory response to ERT or chaperone therapy and there are no curative treatments. Males with classic disease tend to progress despite treatment and the experts indicated that 1% to 5% of this subpopulation develop ADAs that make ERT futile. Other issues include the high cost of ERT and migalastat and the burden associated with ERT, which typically involves biweekly IV infusions that can last a few hours and have the potential for IRRs (estimated to occur in up to 30% of patients). Moreover, some symptoms (fatigue, neuropathic pain, gastrointestinal symptoms, hearing loss, and vertigo) have no treatment, can be difficult to treat, or are slow to respond to therapy. The experts stated that there is a need for treatment that is more effective, has less burdensome administration (e.g., oral drug or less frequent infusions), works for all forms of FD regardless of genetic variant, has few adverse reactions (including a low incidence of ADA development), and crosses the blood-brain barrier.

As per the clinical experts consulted for this review, pegunigalsidase alfa would be used as a first-line therapy, similar to other ERTs that are currently available, and is not expected to change the treatment paradigm for FD. The experts also indicated that it would not be necessary for patients to try other treatments before accessing pegunigalsidase alfa; the drug is not reserved solely for patients with contraindications or intolerance to other treatments. It was also noted that specific therapies for FD are not combined due to cost and other factors, despite the theoretical potential for better outcomes through using multiple mechanisms of action.

The clinical experts stated that adults with a confirmed FD diagnosis and a clear indication for disease-specific therapy could receive pegunigalsidase alfa. Indications for treatment include evidence of kidney or heart disease, stroke, intractable neuropathic pain, or gastrointestinal symptoms. The experts noted that treatment eligibility for FD in Canada is largely determined by, but not exclusive to, the Canadian Fabry Disease Guidelines and the CFDI steering committee.

As per the clinical experts consulted for this review, patients with severe disease are most in need of therapy. These patients tend to be male; to have limited or no residual enzyme activity, elevated plasma lyso-Gb3 levels, and/or a severe *GLA* variant; be older than 50 years of age; to have a low eGFR with advanced renal disease; to have proteinuria of 1.0 g per day or greater; and to have advanced cardiac disease with myocardial fibrosis, dysrhythmias, prior stroke, and high-titre IgG neutralizing ADAs.

Response to treatment may be assessed through stabilization of the eGFR slope, CKD stage, and LVMI; reduction in the rate of Fabry clinical events and in the Fabry Stabilization Index (FASTEX) score, with improvement in symptoms; increased exercise tolerance; and improved work or school attendance and survival. According to the experts, a clinically meaningful response includes a decrease in Fabry clinical event rate; decrease in pain by 1 to 2 points on a 7-point Likert scale; and stabilization of eGFR, CKD stage, left ventricular mass, and New York Heart Association class. Other indicators of treatment response are normalized sweating, return of normal gastrointestinal function, prevention of stroke, and improved HRQoL.

Because FD is a slowly progressing disease, the experts indicated that patients should be followed for at least 2 to 3 years before judging the degree of treatment response and whether the disease is stable or progressing. They also noted that treatment response to ERT varies based on patient characteristics (e.g., age, sex, disease phenotype) and that benefits of ERT may take a year or longer to be realized. In clinical practice, patients are typically seen every 6 to 12 months to monitor treatment and clinical changes, although children and young females who are asymptomatic with normal organ function may be assessed less frequently.

As per the CFDI treatment guidelines, discontinuation of disease-specific treatment should be considered in a patient whose disease is not responding to treatment after at least 1 year, who has persistent and severe IRRs (despite prophylaxis) or IgE ADAs, or when life expectancy is estimated to be less than 1 year. Other reasons for discontinuation include permanent and severe neurocognitive decline, severe reduction in HRQoL or functional status, lack of response to therapy for organ involvement that mandated treatment initiation, poor adherence, and elevated plasma lyso-Gb3 that does not decline. The experts also discussed practical aspects that should be considered, such as the patient's age and burden of ERT compared to the benefit received from treatment. One expert stated that although there is guidance and suggested criteria for stopping treatment, these discussions are difficult once a patient has begun treatment and they want to continue treatment. They also stated that there are older adults who are not eligible for (but would prefer) oral migalastat and decline ERT due to the burden of IV infusions.

Most patients in Canada receive ERT in an outpatient setting, either at home or at an infusion clinic. The clinical experts stated that private nursing services that provide outpatient infusions are paid for by the ERT manufacturer. As with other ERTs, it is recommended that the first 6 to 10 infusions of pegunigalsidase alfa are administered in a hospital outpatient department or infusion clinic due to the risk of IRRs. Once deemed appropriate, most patients can receive at-home infusions.

Various specialists are involved in the diagnosis, treatment, and monitoring of FD, including medical geneticists, nephrologists, cardiologists, neurologists, general internists, pediatricians, and metabolic specialists. The clinical experts stated that patients are best served in a centre of excellence where FD specialists are available. It was also noted that the associated costs of infusions, ADA testing, and lyso-Gb3 monitoring should be covered by the sponsor or the drug plans because the current lack of coverage poses a significant barrier to effective FD care.

Clinician Group Input

Four clinicians, on behalf of the CFDI, submitted written input. The clinicians presented their assessment of peer-reviewed studies on FD, information from the CFDI registry, and input based on their professional expertise.

The clinician group described the main unmet needs, which were the clinical efficacy of existing treatment and the need to reduce the frequency of ERT infusions. According to the clinician group, treatment goals for FD are delaying dialysis and heart failure. They noted that there are other disease manifestations that are difficult to target with drugs, including abdominal pain, neuropathic pain, stroke, and mental health problems.

In addition, cardiac disease in patients continues to progress, including high rates of atrial fibrillation and other arrhythmias, heart failure, and chest pain.

If pegunigalsidase alfa was available in Canada, the clinician group believed that it would provide an alternative form of ERT at the 1 mg/kg dose, but it would not be expected to impact how treatment decisions are made. They noted that the drug may prove to be useful for some adult males with FD and high-titre neutralizing ADAs and a reduced response to therapy.

The clinician group noted that reasons to stop treatment are outlined in the treatment guidelines and are consistent with that described by the clinical experts consulted for this review.

The clinician group recommended that FD be managed by a specialist with experience with the disease, which was consistent with what was suggested by the clinical experts consulted for this review.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for pegunigalsidase alfa:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- system and economic issues.

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

Implementation issues	Response
Relevant comparators	
Both agalsidase beta and agalsidase alfa received negative recommendations from CDA-AMC but are reimbursed in some jurisdictions through exceptional access programs and funding programs for drugs for rare diseases. Eligibility may be based on criteria outlined in the Canadian Fabry Disease Treatment Guidelines, with patient assessment via the CFDI.	Comment from the drug program to inform CDEC deliberations.
Considerations for initiation of therapy	
BALANCE and BRIDGE included patients aged 18 to 60 years. Should patients aged younger than 18 years or older than 60 years be eligible?	The clinical experts stated that patients aged 18 years or older could receive treatment with pegunigalsidase alfa for FD. One expert indicated that pediatric patients aged 17 years or younger could also receive the drug for FD, while another expert noted that adequate evidence of safety and efficacy in pediatric patients would be needed before the drug is used in this population.

Implementation issues	Response
	CDEC noted that the Health Canada indication is for long-term treatment of adult patients with a confirmed diagnosis of FD.
Consider alignment with initiation criteria used by plans for other ERT or migalastat, as appropriate.	Comment from the drug program to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
Consider alignment with renewal criteria used by plans for other ERT or migalastat, as appropriate.	Comment from the drug program to inform CDEC deliberations.

CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CFDI = Canadian Fabry Disease Initiative; ERT = enzyme replacement therapy; FD = Fabry disease.

Clinical Evidence

Systematic Review

Description of Studies

One phase III, double-blind, noninferiority RCT (BALANCE; N = 78) evaluated the efficacy and safety of pegunigalsidase alfa (n = 53) compared to agalsidase beta (n = 25), both at a dosage of 1 mg/kg every 2 weeks, in adult patients with FD. The BALANCE study was originally designed to test the noninferiority of pegunigalsidase alfa to agalsidase beta at the 12-month interim analysis and superiority of the former at the 24-month final analysis. After agalsidase beta was given full market authorization in March 2021 and in consultation with the FDA (September 9, 2021), demonstrating superiority after 24 months was no longer required and noninferiority was assessed at the final analysis at a noninferiority margin for eGFR by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula of $-3 \text{ mL/min/1.73 m}^2$ per year. Efficacy was assessed through the primary end point of median annualized change (slope) in CKD-EPI eGFR over the 2-year study period and other clinically relevant outcomes included incidence of Fabry clinical events, LVMI, and measures of pain. Other outcomes relating to kidney health, exercise tolerance, pain medication use, plasma lyso-Gb3, and patient-reported outcomes were included as supportive evidence (GRADE was not applied).

The BALANCE study included only adults with confirmed FD and reduced kidney function who had at least 1 year of treatment (stable dose for at least 6 month) with agalsidase beta, 1 mg/kg every 2 weeks, before the study. The mean age of patients was 43.9 years (SD = 10.2 years) in the pegunigalsidase alfa group and 45.2 years (standard deviation [SD] = 9.6 years) in the agalsidase beta group. There were more males than females in both treatment groups (by study design) and more than half of patients had classic disease. A larger proportion of patients in the pegunigalsidase alfa group (36.5%) compared to the agalsidase beta group (24.0%) had an eGFR slope greater than $-5 \text{ mL/min/1.73 m}^2$ per year (i.e., had slower decline in kidney function) and proportionately fewer patients in the pegunigalsidase alfa group compared to the agalsidase beta group were receiving treatment with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) (50.0% versus 64.0%).

Efficacy Results

Incidence of Fabry Clinical Events

Fabry clinical events were classified into 4 categories: renal events (first occurrence of either initiation or chronic dialysis [> 40 days], renal transplant), cardiac events (cardiac-related death, myocardial infarction, first-time congestive heart failure, atrial fibrillation, ventricular tachycardia, evidence of progressive heart disease severe enough to require a pacemaker, implantation of pacemaker, bypass surgery, coronary artery dilatation, implantation of defibrillator), cerebrovascular events (hemorrhagic or ischemic stroke, TIA), and death due to non-cardiac-related causes. Overall, Fabry clinical events combined the 4 categories into a composite end point.

In the BALANCE study, 9 (17.3%) patients in the pegunigalsidase alfa group and 2 (8.0%) patients in the agalsidase beta group experienced a Fabry clinical event. In the pegunigalsidase alfa group, 6 patients had 7 cardiac events (atrial fibrillation, angina pectoris, increased troponin, and second-degree atrioventricular block), 3 patients had 3 cerebrovascular events (TIA and cerebrovascular accident), and 1 patient had a renal event (end-stage renal disease necessitating a kidney transplant). In the agalsidase beta group, 2 patients had 2 cardiac events (ventricular tachycardia requiring a pacemaker and atrial fibrillation).

Annualized Change in CKD-EPI eGFR Slope

The median annual CKD-EPI eGFR slope in the BALANCE study was -2.51 mL/min/ 1.73 m² per year (95% CI, -3.79 mL/min/ 1.73 m² per year to -1.24 mL/min/ 1.73 m² per year) in the pegunigalsidase alfa group and -2.16 mL/min/ 1.73 m² per year (95% CI, -3.81 mL/min/ 1.73 m² per year to -0.51 mL/min/ 1.73 m² per year) in the agalsidase beta group. The treatment group difference was -0.36 mL/min/ 1.73 m² per year (95% CI, -2.44 mL/min/ 1.73 m² per year to 1.73 mL/min/ 1.73 m² per year) for the ITT population and -0.12 mL/min/ 1.73 m² per year (95% CI, -2.45 mL/min/ 1.73 m² per year to 2.21 mL/min/ 1.73 m² per year) for the per-protocol population. Because the lower bound of the 95% CI for the treatment group difference was greater than the prespecified noninferiority margin of -3.0 mL/min/ 1.73 m² per year, the sponsor concluded that pegunigalsidase alfa was noninferior to agalsidase beta.

Left Ventricular Mass Index

One of the cardiac complications of FD is thickening of the left ventricular wall. LVMI was calculated based on left ventricular mass determined by MRI.

At baseline in the BALANCE study, the mean LVMI was 75.97 g/m² (standard error [SE] = 5.13 g/m²) in the pegunigalsidase alfa group and 82.22 g/m² (SE = 6.34 g/m²) in the agalsidase beta group. At week 104, LVMI was 71.56 g/m² (SE = 5.2 g/m²) in the pegunigalsidase alfa group and 82.43 g/m² (SE = 8.39 g/m²) in the agalsidase beta group. The mean change from baseline was -0.64 g/m² (SE = 2.69 g/m²) in the pegunigalsidase alfa group and 0.29 g/m² (SE = 3.73 g/m²) in the agalsidase beta group. The difference between treatment groups was -0.92 g/m² (95% CI, -10.26 g/m² to 8.42 g/m²).

BPI-Short Form Score

In the BPI-Short Form, patients rate the severity of their pain from 0 to 10 points (from no pain to worst imaginable pain) and how the pain impacts their general activity, mood, walking, working, sleeping, relations

with other people, and enjoyment of life from 0 to 10 (from does not interfere to completely interferes) for 9 pain-related questions. Scores are generated for pain at its worst in the past 24 hours, pain at its least in the past 24 hours, pain right now, and pain on average. Scores from 1 to 4 points indicate mild pain, 5 or 6 indicate moderate pain, and 7 to 10 indicate severe pain.

In the BALANCE study, the mean change from baseline to week 104 for pain at its worst was -0.1 points (SE = 0.5 points) in the pegunigalsidase alfa group and 0.6 points (SE = 0.6 points) in the agalsidase beta group. The treatment group difference was -0.7 points (95% CI, -2.2 to 0.8 points).

The mean change from baseline to week 104 for pain at its least was 0.2 points (SE = 0.3 points) in the pegunigalsidase alfa group and 0.1 points (SE = 0.4 points) in the agalsidase beta group. The treatment group difference was 0.1 points (95% CI, -1.0 to 1.1 points).

The mean change from baseline to week 104 for current pain was 0.1 points (SE = 0.4 points) in the pegunigalsidase alfa group and 0.1 points (SE = 0.5 points) in the agalsidase beta group. The treatment group difference was -0.1 points (95% CI, -1.4 to 1.2 points).

The mean change from baseline to week 104 for average pain was 0.4 points (SE = 0.3 points) in the pegunigalsidase alfa group and 0.2 points (SE = 0.4 points) in the agalsidase beta group. The treatment group difference was 0.2 points (95% CI, -0.9 to 1.2 points).

Health-Related Quality of Life

There was no information on HRQoL in the BALANCE study.

Other Efficacy Results

Plasma lyso-Gb3 concentration, urine protein creatinine ratio (UPCR) category, Mainz Severity Score Index (MSSI) overall score, exercise stress test score, pain medication use, and EQ-5D-5L score were considered clinically relevant and to be supporting evidence in the BALANCE study.

Harms Results

Treatment-emergent adverse events (TEAEs) were reported by 47 (90.4%) patients in the pegunigalsidase alfa group and 24 (96.0%) patients in the agalsidase beta group in the BALANCE study. The most common TEAEs in the pegunigalsidase alfa and agalsidase beta groups were headache (21.2% and 20.0%), nasopharyngitis (21.2% and 16.0%), diarrhea (19.2% and 24.0%), back pain (15.4% and 20.0%), cough (11.5% and 20.0%), and bronchitis (9.6% and 20.0%). Eight (15.4%) patients in the pegunigalsidase alfa group reported 14 serious adverse events (SAEs) and 6 (24.0%) patients in the agalsidase beta group reported 11 SAEs. Two patients stopped treatment due to TEAEs (IRR and multiple events); both were in the pegunigalsidase alfa group. There were no deaths in the study.

There were 6 (11.5%) patients in the pegunigalsidase alfa group and 3 (12.0%) patients in the agalsidase beta group who experienced an injection site reaction. Of the 11 (21.2%) patients who reported any IRRs in the pegunigalsidase alfa group, 11 patients reported mild or moderate IRRs and 1 patient reported a severe or very severe IRR. Of the 6 (24.0%) patients reporting IRRs in the agalsidase beta group, all 6 patients reported mild or moderate IRRs. There were 6 (11.5%) patients in the pegunigalsidase alfa group and 5

(20.0%) patients in the agalsidase beta group who reported treatment-emergent ADAs. Of the 20 patients in the pegunigalsidase alfa group who had ADAs during any postbaseline visit in the study, 15 (75.0%) had neutralizing ADAs. Of the 11 patients in the agalsidase beta group who had ADAs during the study, 9 (81.8%) had neutralizing ADAs.

Critical Appraisal

Randomization was stratified by baseline UPCR and no other characteristics, of which there are many that impact FD outcomes. There were notable imbalances in the baseline characteristics between treatment groups, most of which point toward the pegunigalsidase alfa group having less severe disease and better kidney function and biases in favour of pegunigalsidase alfa. Imbalances may also be a result of the small study size (which is understandable due to the rarity of the condition) and the heterogeneity of FD.

BALANCE was a noninferiority study aiming to determine if pegunigalsidase alfa was noninferior to agalsidase beta for annualized eGFR slope over 2 years at a noninferiority margin of $-3.0 \text{ mL/min/1.73 m}^2$ per year. The noninferiority margin was based on natural history data for patients with FD and on the European expert consensus statement on therapeutic goals in Fabry disease. However, the FDA noted that the margin is unreliable for informing noninferiority due to the natural history data being from a clinically different population than in the BALANCE study (where according to the FDA, the natural history data were based on untreated, male patients and the data cannot be adjusted for differences in the BALANCE population), and the methodology for choosing the margin (i.e., it was not based on preserving an established minimum treatment effect for agalsidase beta versus placebo in a population similar to that in the BALANCE study). The FDA examined assay sensitivity using external data to support the expected treatment effect of agalsidase beta in the BALANCE study population and to help contextualize the study results with an unreliable noninferiority margin; however, the noninferiority of pegunigalsidase alfa to agalsidase beta remains uncertain. Based on expert opinion and information from the literature, a smaller margin would be more appropriate, such as $-1 \text{ mL/min/1.73 m}^2$ per year, which is the eGFR slope of healthy populations aged 40 years and older, a treatment goal for patients with FD, and has been suggested as a clinically meaningful difference in mean eGFR slopes for patients with CKD.

There were differences between the 2 treatment groups in concomitant medication use, study withdrawals, and critical or major protocol deviations, all of which can bias toward a conclusion of noninferiority. However, the results for the ITT ($N = 77$) and per-protocol ($N = 72$) analyses were similar, which supports the sponsor's claim of noninferiority for the chosen margin. Although this was a noninferiority study, there were no noninferiority margins provided for the secondary outcomes, and clinical meaningfulness was informed by clinical expert opinion or MIDs that have not been verified in FD. In the BALANCE study, there were data missing for every outcome, there was no imputation for those data, and they were assumed to be missing at random, which is untestable and unlikely for all patients, which would add further uncertainty to the results. eGFR slope and LVMI, although objective outcomes, require years to produce a reliable estimate and vary based on patient and disease characteristics.

The BALANCE study population does not represent the full spectrum of patients who could receive pegunigalsidase alfa in practice. There are pediatric and older adult patients who could be eligible for ERT

but were not represented in the study. Additionally, not all patients with FD have kidney involvement (e.g., those with late-onset FD and cardiac variants), but still need to be treated. All patients in the study had prior treatment experience, which may inform treatment switching; however, this drug could be used in patients without prior treatment experience. There is also a risk of selection bias for patients who could tolerate the clinical and nonclinical aspects of ERTs (premedication, travel to an infusion centre, IRRs, duration of infusion, and biweekly administration). The eligibility criteria in the BALANCE study did not include patients with poorer health who might receive the drug in clinical practice in Canada, such as those undergoing renal dialysis or postrenal transplant, those with proteinuria not receiving ACEi or ARB treatment, and those with prior cardiovascular events or heart failure. It is worth noting that the Health Canada indication for pegunigalsidase alfa is for the long-term treatment of adult patients with a confirmed diagnosis of FD; it does not mention the need for patients to have symptoms of end organ involvement, as noted in the CFDI treatment guidelines. Input from patient and clinician groups highlighted the need for treatments that slow disease progression and improve clinical outcomes as well as FD symptoms and HRQoL. The BALANCE study provides information on how pegunigalsidase alfa impacts Fabry clinical events, renal function, aspects of cardiac health, and pain, but there was a lack of evidence supporting improvement of gastrointestinal issues and HRQoL. The BALANCE study also does not inform on long-term use of pegunigalsidase alfa or long-term comparability to other treatments.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE 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.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

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.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- incidence of Fabry clinical events
- annualized change in CKD-EPI eGFR (slope)
- LVMI (g/m²) by MRI
- BPI-Short Form score
- IRRs and ADAs.

Table 3: Summary of Findings for Pegunigalsidase Alfa vs. Agalsidase Beta for Patients With Fabry Disease

Outcome and follow-up	Patients (studies), N	Absolute effects			Certainty	What happens
		Agalsidase beta	Pegunigalsidase alfa	Difference		
Fabry clinical events						
Incidence of overall Fabry clinical events, n (%) Follow-up: 104 weeks	77 (1 RCT)	2 (8.0)	9 (17.3)	93 more per 1,000 (95% CI, 104 fewer per 1,000 to 243 more per 1,000)	Very low ^a	The evidence is very uncertain about the effect of pegunigalsidase alfa on overall Fabry clinical events when compared with agalsidase beta.
Annualized CKD-EPI eGFR slope						
Annual CKD-EPI eGFR slope (mL/min/1.73 m ²), median Follow-up: 104 weeks	76 (1 RCT)	−2.16 (95% CI, −3.81 to −0.51)	−2.51 (95% CI, −3.79 to −1.24)	−0.36 (95% CI, −2.44 to 1.73)	Very low ^b	The evidence is very uncertain about the effect of pegunigalsidase alfa on annualized CKD-EPI eGFR slope when compared with agalsidase beta.
LVMI by MRI						
LVMI (g/m ²), mean Follow-up: 104 weeks	47 (1 RCT)	0.29 (SE = 3.73)	−0.64 (SE = 2.69)	−0.92 (95% CI, −10.26 to 8.42)	Very low ^c	The evidence is very uncertain about the effect of pegunigalsidase alfa on LVMI when compared with agalsidase beta.
Patient-reported outcomes						
BPI-Short Form score for average pain (points): 0 (no pain) to 10 (worst imaginable pain), mean Follow-up: 104 weeks	67 (1 RCT)	0.2 (SE = 0.4)	0.4 (SE = 0.3)	0.2 (95% CI, −0.9 to 1.2)	Very low ^d	The evidence is very uncertain about the effect of pegunigalsidase alfa on average pain based on the BPI-Short Form when compared with agalsidase beta.
HRQoL	NA	NA	NA	NA	NA	There is no evidence for the effect of pegunigalsidase alfa on HRQoL.

Outcome and follow-up	Patients (studies), N	Absolute effects			Certainty	What happens
		Agalsidase beta	Pegunigalsidase alfa	Difference		
Harms						
Severe or very severe IRRs, incidence Follow-up: 104 weeks	77 (1 RCT)	0 per 1,000	19 per 1,000	19 more per 1,000 (95% CI, 122 fewer to 107 more per 1,000)	Low ^e	Pegunigalsidase alfa may result in an increase in the incidence of severe or very severe IRRs when compared with agalsidase beta. The clinical importance of the increase is unclear.
Neutralizing ADAs, incidence Follow-up: 104 weeks	77 (1 RCT)	818 per 1,000	750 per 1,000	68 fewer per 1,000 (95% CI, 360 fewer to 293 more per 1,000)	Moderate ^f	Pegunigalsidase alfa likely results in a reduction in the incidence of neutralizing ADAs when compared with agalsidase beta. The clinical importance of the reduction is unclear.

ADA = antidrug antibody; BPI = Brief Pain Inventory; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FD = Fabry disease; HRQoL = health-related quality of life; IRR = infusion-related reaction; LVMI = left ventricular mass index; NA = not applicable; NI = noninferiority; RCT = randomized controlled trial; SE = standard error.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aRated down 1 level for study limitations (imbalances in baseline characteristics increases the potential for bias in results favouring pegunigalsidase alfa). Rated down 1 level for indirectness (all patients had experience with agalsidase beta before the BALANCE study and the Health Canada indication does not restrict to only patients with previous treatment; no patients older than 60 years were included; all patients had to have evidence of kidney function decline, which is not a characteristic of all patients with FD who require treatment; patients with poorer health, who would be treated in practice, were not included). Rated down 1 level for imprecision (there was no known threshold for a clinically important effect and the presence of an important effect was informed by expert opinion for this review; the results are difficult to interpret due to the small number of events, wide CI, and the 2-year follow-up that is relatively short for clinical outcomes that may take years to develop). Analysis of this outcome was not adjusted for multiplicity, and the results are considered supportive evidence.

^bRated down 1 level for study limitations (imbalances in baseline characteristics increases the potential for bias in results favouring pegunigalsidase alfa). Rated down 1 level for indirectness (all patients had experience with agalsidase beta before the BALANCE study and the Health Canada indication does not restrict to only patients with previous treatment; no patients older than 60 years were included; all patients had to have evidence of kidney function decline, which is not a characteristic of all patients with FD who require treatment; patients with poorer health, who would be treated in practice, were not included). Rated down 1 level for imprecision. While NI was reached based on the sponsor-suggested NI margin. However, regulatory agencies have rejected the suggested NI margin and indicated that a smaller margin would be more appropriate. Based on expert opinion and evidence from the literature, a NI margin or meaningful difference of $-1 \text{ mL/min/1.73 m}^2$ per year would indicate that pegunigalsidase alfa is potentially meaningfully worse or better than agalsidase beta, based on the lower and upper bounds of the 95% CI.

^cRated down 1 level for study limitations (imbalances in baseline characteristics increases the potential for bias in results favouring pegunigalsidase alfa and a notable amount of missing data biases toward an NI conclusion). Rated down 1 level for indirectness (all patients had experience with agalsidase beta before the BALANCE study and the Health Canada indication does not restrict to only patients with previous treatment; no patients older than 60 years were included; patients with poorer health, who would be treated in practice, were not included). Rated down 2 levels for imprecision (there was no known threshold for a clinically important effect and the presence of an important effect was informed by expert opinion for this review; based on expert opinion for a clinically meaningful threshold, the bounds of the 95% CI suggest the possibility of both a meaningful improvement or worsening in LVMI). Analysis of this outcome was not adjusted for multiplicity, and the results are considered supportive evidence.

^dRated down 1 level for study limitations (imbalances in baseline characteristics increases the potential for bias in results favouring pegunigalsidase alfa and a notable amount of missing data biases toward an NI conclusion). Rated down 1 level for indirectness (all patients had experience with agalsidase beta before the BALANCE study and the Health Canada indication does not restrict to only patients with previous treatment; no patients older than 60 years were included; patients with poorer health, who would be treated in practice, were not included). Rated down 1 level for imprecision (the estimated threshold for a clinically important effect ranges from 1 to 2 points [but has not been verified in FD]; the bounds of the 95% CI approach or cross the estimated clinically meaningful threshold and suggest the possibility of both a meaningful improvement or worsening in average pain compared to agalsidase beta). Analysis of this outcome was not adjusted for multiplicity, and the results are considered supportive evidence.

*Rated down 1 level for indirectness (all patients had experience with agalsidase beta before the BALANCE study and the Health Canada indication does not restrict to only patients with previous treatment; no patients older than 60 years were included; all patients had to have evidence of kidney function decline, which is not a characteristic of all patients with FD who require treatment; patients with poorer health, who would be treated in practice, were not included). Rated down 1 level for imprecision (there was no known threshold for a clinically important effect, and the presence of an important effect was informed by expert opinion for this review; few events were observed and there were inadequate data to inform a higher certainty judgment). Analysis of this outcome was not adjusted for multiplicity, and the results are considered supportive evidence.

†Rated down 1 level for indirectness (all patients had experience with agalsidase beta before the BALANCE study and the Health Canada indication does not restrict to only patients with previous treatment; no patients older than 60 years were included; all patients had to have evidence of kidney function decline, which is not a characteristic of all patients with FD who require treatment; patients with poorer health, who would be treated in practice, were not included). Analysis of this outcome was not adjusted for multiplicity, and the results are considered supportive evidence.

Source: Clinical Study Report for BALANCE and sponsor’s Summary of Clinical Evidence. Details included in the table are from the sponsor’s Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

Additional studies submitted by the sponsor provided evidence in patients without ERT experience as well as an additional OLE study that included patients with and without ERT experience.

PB-102-F01 (F01 study) and PB-102-F02 (F02 study) were open-label, multicentre, dose-ranging, single-arm studies of adults with symptomatic FD who had either never received ERT or had not received it within the past 6 months. Enrolment in the F02 study required prior completion of the F01 study. Interventions were pegunigalsidase alfa dosages of 0.2 mg/kg, 1.0 mg/kg, or 2.0 mg/kg via IV every 2 weeks for 12 weeks (F01 study) or for 36 weeks (F02 study). Outcomes of interest were annualized eGFR slope, pain as measured with the BPI-Short Form, and harms. Safety results revealed that pegunigalsidase alfa had an acceptable safety profile. Most TEAEs were mild or moderate in severity, and there was a low rate (18.8%) of treatment-induced antibody formation. Results from these trials were consistent with those in the BALANCE and BRIDGE trials.

Patients completing the F01 and F02 studies could enrol in the PB-102-F03 (F03 study) extension study (N = 15). The intervention was pegunigalsidase alfa 1.0 mg/kg via IV every 2 weeks for up to 60 months. The outcomes measured in the F03 study were the same as in the F01 and F02 studies.

At the time of the submission, PB-102-F60 (F60 study) was an ongoing, OLE study evaluating the safety, tolerability, and efficacy of pegunigalsidase alfa 1 mg/kg via IV every other week in adult patients with FD (N = 87 patients, with ongoing enrolment). Patients eligible for the F60 study must have completed the BALANCE study or BRIDGE study or at least 48 months of the F03 study. The total duration of study treatment was up to 60 months, until pegunigalsidase alfa became commercially available, or at the sponsor's discretion. Efficacy outcomes of interest included Fabry clinical events and change from baseline for eGFR, eGFR slope, and BPI-Short Form score. Safety outcomes were evaluated throughout the study, comprising TEAEs, IRRs, and ADAs.

Efficacy Results

Of the [REDACTED] patients enrolled at the interim data cut-off ([REDACTED]), [REDACTED] patients were from the F03 study, [REDACTED] patients from the BRIDGE study, and [REDACTED] patients from the BALANCE study. Overall, only [REDACTED] ([REDACTED]%) patients had discontinued therapy at the time of data cut-off (due to [REDACTED] in [REDACTED]%) patients and [REDACTED] in [REDACTED] ([REDACTED]%) patients). Overall, [REDACTED] ([REDACTED]%) patients completed the scheduled week 52 visit.

Incidence of Fabry Clinical Events

Overall, [REDACTED] ([REDACTED]%) patients reported [REDACTED] up to the data cut-off date. [REDACTED] were the most common ([REDACTED]%), followed by [REDACTED] ([REDACTED]%), and [REDACTED] ([REDACTED]%). There were no [REDACTED]. Overall, there was a [REDACTED].

Annualized Change in CKD-EPI eGFR Slope

Annualized eGFR slopes were estimated for each patient with at least 1 year of follow-up. The mean annualized eGFR slope in the ITT population was [REDACTED] mL/min/1.73 m² per year (SE = [REDACTED] mL/min/1.73 m² per year). The mean annualized eGFR slope was [REDACTED] mL/min/1.73 m² per year [SE = [REDACTED] mL/min/1.73 m² per year]) than [REDACTED] [REDACTED] mL/min/1.73 m² per year [SE = [REDACTED] mL/min/1.73 m² per year]).

Left Ventricular Mass Index

LVMI results were not available from the interim analysis for the F60 study.

BPI-Short Form

Pain severity domain results at week 52 in the overall ITT population had a mean change from baseline to week 52 of [REDACTED] points (SE = [REDACTED] points) for worst pain, [REDACTED] points (SE = [REDACTED] points) for least pain, [REDACTED] points (SE = [REDACTED] points) for pain right now, and [REDACTED] points (SE = [REDACTED] points) for average pain.

The BPI-Short Form scores were [REDACTED] at baseline and week 52 in pain severity domains (mean changes [REDACTED] points) and pain interference domains (mean changes [REDACTED] points) based on [REDACTED] of [REDACTED] patients. Most patients with data in the ITT population ([REDACTED] of [REDACTED] patients [REDACTED]%) had a [REDACTED] [REDACTED] in average pain severity at week 52 compared to baseline.

Other Efficacy Results

Plasma lyso-Gb3, UPCR, MSSI score, and EQ-5D-5L score were considered clinically relevant and supporting evidence.

Harms Results

By week 52, [REDACTED]% of patients reported at least 1 TEAE, [REDACTED]% reported at least 1 SAE, [REDACTED]% discontinued treatment due to a TEAE, and [REDACTED]% of patients died.

A total of [REDACTED] were reported in [REDACTED] ([REDACTED]%) patients. There was [REDACTED] [REDACTED] for a total of [REDACTED] in [REDACTED] ([REDACTED]%) patients.

A total of [REDACTED] ([REDACTED]%) patients in the overall safety population were [REDACTED] at any postbaseline visit in the F60 study up to the interim analysis cut-off. [REDACTED] occurred in [REDACTED] ([REDACTED]%) patients, including [REDACTED] ([REDACTED]%) patients with [REDACTED] and [REDACTED] ([REDACTED]%) patients with [REDACTED].

Critical Appraisal

Patient characteristics in the F60 study aligned with those in the F01, F02, F03, BALANCE, and BRIDGE studies. Overall, the F60 study had a small sample size (N = 87), which is a function of rare disease studies and because of the requirement to have completed the previous studies for enrolment. Having completed the requisite studies, patients enrolled in the F60 study comprised a highly enriched and selected sample. Because [REDACTED] of patients in the F60 study did not have experience with the treatment, a majority of patients were likely to have had positive responses and were able to tolerate pegunigalsidase alfa. The

largest percentage of patients were from the BALANCE study (■■■■ [■■■■%] randomized to pegunigalsidase alfa and ■■■■ [■■■■%] randomized to agalsidase beta). The open-label design of the F60 study meant that patients were not blinded to treatment and may have reported more favourable patient-reported outcomes related to HRQoL and pain and may have been less likely to report TEAEs in the follow-up period because of their awareness of the treatment. Baseline characteristics appeared to be imbalanced between females and males, and the sponsor did not note the percentage of participants with classic FD by sex, which is a key effect modifier. In patients who switched from agalsidase beta to pegunigalsidase alfa, there is the potential for a 6-month carryover effect after discontinuation of a previous treatment, as per the clinical experts consulted for this review. It is unclear if a patient's response to pegunigalsidase alfa was related to their prior drug doses (0.2 mg/kg versus 2.0 mg/kg) used in the F01 and F02 studies before starting at a dose of 1.0 mg/kg in the F60 study. Moreover, the lack of a comparator is a major limitation in this study. The outcomes in the F60 study were the same as the BALANCE study, ■■■■. ■■■■.

Notable harms in the F60 study () were . A possible explanation for the in the F60 study could be attributed to selection bias, in which individuals who previously experienced and in the F01, F02, and F03 studies may have dropped out before enrolling in the F60 study.

The Health Canada indication for pegunigalsidase alfa is for the long-term treatment of adult patients with a confirmed diagnosis of FD, which the F60 study aims to address. Patients enrolled in the F60 study included those previously treated with ERT (from the BALANCE and BRIDGE studies) and █ (████%) patients from the F03 study without treatment experience. Given that █ patients did not have treatment experience, subgroup analyses were not feasible; therefore, the results of the F60 study do not allow for meaningful conclusions to be drawn for this subgroup. Patients who started in the BALANCE study and transitioned to the F60 study could have switched from agalsidase beta 1 mg/kg (n = █; █%) to pegunigalsidase alfa 1 mg/kg. According to the experts, the practice of switching between ERTs varies among physicians; therefore, the results from patients who switched ERTs have limited external generalizability, particularly in clinical settings in which patients do not typically switch ERTs. Based on the clinical experts consulted for this review, due to the X-linked nature of FD, males typically have earlier disease onset, more serious disease, and a poorer prognosis. Therefore, females with FD who enrol in clinical studies tend to have better clinical outcomes relative to males. Because the F60 study included 55 males and 32 females, the study had a lower proportion of participants with an expected worse prognosis than would be anticipated based on the estimated relative frequency of FD in the general population (1 in 40,000 in males and 1 in 117,000 in females).

Indirect Comparisons

Description of Studies

There is an absence of direct comparative efficacy and safety evidence between pegunigalsidase alfa and disease-specific treatments for FD, other than agalsidase beta. To address this, the sponsor submitted an NMA using a Bayesian framework comparing pegunigalsidase alfa to agalsidase beta, agalsidase alfa, and migalastat. Outcomes of interest included change in eGFR, LVMI, BPI score, and ADAs.

In addition, the sponsor submitted unanchored population-adjusted indirect comparisons (PAICs) using simulated treatment comparison methods to adjust for population differences between patients receiving pegunigalsidase alfa in the BALANCE, F01, F02, F03, and BRIDGE studies and patients receiving comparator treatments. Regression models suitable for outcome type were fitted to individual patient data of those treated with pegunigalsidase alfa, adjusting for covariates based on treatment effect modifiers and prognostic variables at baseline in the comparator trials. Adjustments could only be made for differences in treatment exposure status, age, sex, phenotype, migalastat-amenable variant status, and baseline eGFR, depending on the data available for each outcome. Due to the limitations of unanchored PAICs, the results have not been reported or discussed in this review, and only the results of the Bayesian framework are presented.

Efficacy Results

From the systematic literature review, there were 120 records from 56 original studies; after study eligibility was applied, 7 studies were included in the NMA. For all outcomes of interest, there were only single studies comparing any 2 treatments so a random-effects model could not be estimated; therefore, the results are based on the fixed-effects model.

Change From Baseline in eGFR

The mean difference in change from baseline in eGFR between pegunigalsidase alfa and the comparators was [REDACTED] mL/min/1.73 m² (95% CrI, [REDACTED] mL/min/1.73 m²) for agalsidase beta after 104 weeks of treatment, [REDACTED] mL/min/1.73 m² (95% CrI, [REDACTED] mL/min/1.73 m²) for agalsidase alfa after 52 weeks of treatment, and [REDACTED] mL/min/1.73 m² (95% CrI, [REDACTED] mL/min/1.73 m²) for migalastat after 26 weeks of treatment. [REDACTED]

Left Ventricular Mass Index

The mean difference in LVMI between pegunigalsidase alfa and the comparators was 3.82 g/m² (95% CrI, -1.26 g/m² to 8.91 g/m²) for agalsidase beta after 104 weeks of treatment, 21.00 g/m² (95% CrI, -21.68 g/m² to 63.73 g/m²) for agalsidase alfa after 52 weeks of treatment, and 28.69 g/m² (95% CrI, -34.01 g/m² to 91.38 g/m²) for migalastat after 26 weeks of treatment. The sensitivity analyses that removed the real-world evidence study and combined the 2 doses of agalsidase beta supported the base case.

Brief Pain Inventory

The mean difference for BPI score between pegunigalsidase alfa and the comparators was [REDACTED] points (95% CrI, [REDACTED] points) for agalsidase beta after 104 weeks of treatment and [REDACTED] points (95% CrI, [REDACTED] points) for agalsidase alfa after 24 weeks of treatment.

Harms Results

Antidrug Antibodies

The odds ratio of a patient developing ADAs was [REDACTED] (95% CrI, [REDACTED]), [REDACTED], and [REDACTED] (95% CrI, [REDACTED]), [REDACTED].

Critical Appraisal

If the network was unconnected or there were important differences in treatment effect modifiers between studies, PAICs were considered. Although the sponsor attempted to adjust for important treatment effect modifiers and prognostic variables to control the risk of bias, data were unreported for many characteristics. It was not possible to adjust for ADA status, ACEi or ARB treatment, UPCR category, baseline left ventricular hypertrophy status, migalastat-amenable variant status, genotype, and lyso-Gb3 concentration. Most of the studies in the PAICs enrolled a small number of patients (fewer than 30 patients), and there were very limited patient-level data for those who did not have treatment experience ($n = 6$) or who had a migalastat-amenable variant ($n = 9$). Therefore, the unanchored PAICs using simulated treatment comparison methods have limitations, putting their results at high risk of bias that increase the uncertainty of the comparisons; therefore, these results have not been reported in this review. The uncertainties in the validity of the unanchored comparisons have also been acknowledged in the sponsor-submitted ITC report.

The overall network was sparse because it included few drugs and few comparative trials. All studies included a small number of patients, which is understandable because FD is rare; most of these studies had fewer patients than the BALANCE study (as few as 15 patients). For the outcomes of interest for the report, a random-effects model was not estimable; therefore, the comparisons used a fixed-effects model. Use of only a fixed-effects model, along with the wide CrIs, leads to a high level of uncertainty in the estimates.

To connect pegunigalsidase alfa and agalsidase alfa within some outcome networks, the normal and low doses of agalsidase beta had to be combined. This required the assumption of similar efficacy and safety to be made, which is unlikely to be true and may introduce bias that cannot be adjusted for. Moreover, the lower doses of agalsidase beta are not used in clinical practice according to the clinical experts consulted for this review.

For the results of a NMA to be valid, the studies and patients included in the network must be sufficiently similar; however, there were clear differences in study dates, study design, geographic location, treatment duration, outcome assessment time points, and permission to switch treatments. There was also variability in study eligibility criteria, which produced notably different study populations. This was confirmed when looking at the baseline characteristics across studies. There were differences in mean age, sex, mean baseline eGFR, and prior treatment exposure. Many characteristics that were identified as treatment effect

modifiers were not reported across all studies, such as disease phenotype, migalastat-amenable variant, left ventricular hypertrophy, mean UPCR, and presence of ADAs. Moreover, dosages of migalastat and agalsidase beta in some studies were inconsistent with the Health Canada product monographs. There was also imputation of missing study values using data from the BALANCE study, potential variability in outcome assays or measurements (even for objective outcomes such as eGFR and LVMI), and inconsistency in outcome definitions and time points. Overall, there were important differences across studies that cannot be adjusted for using NMA methods.

Due to the differences in study designs, study populations, comparator doses, and outcomes, the transitivity assumption is likely not valid. Homogeneity of treatment effect could not be assessed because there were only single studies informing relevant direct comparisons (i.e., between active treatments for FD). Consistency of treatment effect could not be assessed because there were no closed loops that contained pegunigalsidase alfa.

Outcomes of interest to patients and clinicians that were missing include eGFR slope, HRQoL, and IRRs. For eGFR slope and IRRs, an attempt was made to create networks, but it was not possible to connect pegunigalsidase alfa with agalsidase alfa or migalastat. Due to the lack of evidence from the ITC, it is unknown how these drugs compare for these outcomes. Study durations varied and the long-term treatment effects are uncertain based on the results of the NMA.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

BRIDGE (N = 22) was a phase III, open-label, switch-over study evaluating the safety and efficacy of pegunigalsidase alfa, 1 mg/kg every 2 weeks, in adults with FD who were previously treated for at least 2 years with agalsidase alfa at a stable dose for at least 6 months. This study was included to address a gap in the evidence for patients treated with pegunigalsidase alfa who were not previously treated with agalsidase beta (as in the BALANCE study).

Eligibility criteria were similar to those in the BALANCE study, except that all patients had to have prior treatment with agalsidase alfa in the BRIDGE study. Pegunigalsidase alfa was administered at a dosage consistent with that used in the BALANCE study for 12 months, and study outcomes were also consistent with the BALANCE study.

Of the 22 patients enrolled in the BRIDGE study, 20 (90.9%) completed 12 months of treatment. There were 2 discontinuations due to TEAEs. The mean age of patients was 44.0 years (SD = 11.0 years). There were more males (68.2%) than females (31.8%), as per the study design, and more than half of patients had classic FD (63.6%). Mean eGFR was 82.5 mL/min/1.73 m² (SD = 23.4 mL/min/1.73 m²), and mean eGFR slope was -5.3 mL/min/1.73 m² per year (SD = 6.3 mL/min/1.73 m² per year). Mean exposure time to pegunigalsidase alfa was 11.0 months (SD = 3.5 months) in the study.

Efficacy Results

Incidence of Fabry Clinical Events

One patient experienced 2 Fabry clinical events (cardiac event and cerebrovascular event).

Annualized Change in CKD-EPI eGFR Slope

The preswitch mean eGFR slope in the BRIDGE study was -5.90 mL/min/ 1.73 m² per year (SE = 1.34 mL/min/ 1.73 m² per year), based on historical data. The postswitch mean eGFR slope was -1.19 mL/min/ 1.73 m² per year (SE = 1.77 mL/min/ 1.73 m² per year).

Left Ventricular Mass Index

Of the 19 patients who contributed to the analysis in the BRIDGE study, LVMI was 86.9 g/m² (SE = 6.9 g/m²) at baseline and 89.4 g/m² (SE = 6.1 g/m²) at month 12. The change from baseline to month 12 was 4.1 g/m² (SE = 2.8 g/m²).

BPI-Short Form Score

In the BRIDGE study, the mean score for pain at its worst in the past 24 hours was [REDACTED] points (SE = [REDACTED] points) at baseline and [REDACTED] points (SE = [REDACTED] points) at month 12. The mean change from baseline was [REDACTED] points (SE = [REDACTED] points). The mean score for pain at its least in the past 24 hours was [REDACTED] points (SE = [REDACTED] points) at baseline and [REDACTED] points (SE = [REDACTED] points) at month 12. The mean change from baseline was [REDACTED] points (SE = [REDACTED] points). The mean score for current pain was [REDACTED] points (SE = [REDACTED] points) at baseline and [REDACTED] points (SE = [REDACTED] points) at month 12. The mean change from baseline was [REDACTED] points (SE = [REDACTED] points). The mean score for average pain was [REDACTED] points (SE = [REDACTED] points) at baseline and [REDACTED] points (SE = [REDACTED] points) at month 12. The mean change from baseline was [REDACTED] points (SE = [REDACTED] points).

Other Efficacy Results

Plasma lyso-Gb3, UPCR, MSSI score, exercise stress test, pain medication use, and EQ-5D-5L score were considered clinically relevant and supporting evidence.

Harms Results

Twenty-one (95.5%) patients in the BRIDGE study reported at least 1 TEAE; the 2 most common were headache reported by 5 patients (22.7%) and nasopharyngitis reported by 7 patients (31.8%). Four (18.2%) patients reported at least 1 SAE, which included 2 hypersensitivity events and 1 event each for infectious mononucleosis and urinary tract infection. Two (9.1%) patients withdrew due to TEAEs; both were IRRs (hypersensitivity reactions). There were no deaths in the study.

For notable harms of interest for this review, 3 (13.6%) patients reported injection site reactions, 5 (22.7%) patients reported IRRs, 7 (31.8%) patients had treatment-emergent ADAs, and 2 (28.6%) of those patients had neutralizing ADAs.

Critical Appraisal

The main limitations of the BRIDGE study were the open-label design and lack of a comparator group. It is possible that knowledge of the treatment impacted subjective outcomes, such as the BPI-Short Form score

and harms reporting. Additionally, uncontrolled confounding puts the results at high risk of bias. Historical values (up to 24 months before screening) were used to estimate the baseline eGFR and these were likely unreliable. All patients in the BRIDGE study had previously received a stable dose of agalsidase alfa prior to the study and there is a possibility of carryover effects during the first few months of the study. This is additionally concerning because the BRIDGE study was only 12 months long and carryover effects can persist for 6 months, according to the clinical experts consulted for this review.

The generalizability concerns discussed for the BALANCE study are largely applicable to the BRIDGE study because the eligibility criteria were very similar. Briefly, the age limits (18 to 60 years), eGFR of at least 40 mL/min/1.73 m², all patients having prior ERT experience for at least 2 years, and the exclusion of patients with poorer health may prevent broad application of the results to those who do not meet these characteristics but could otherwise receive pegunigalsidase alfa in clinical practice. All patients switched from agalsidase alfa to pegunigalsidase alfa and although the choice to switch varies in practice based on clinician and patient preference, the study does not provide information on patients without prior treatment exposure and does not provide an adequate (short-term or long-term) comparison between pegunigalsidase alfa and agalsidase alfa. The outcomes were generally the same as the BALANCE study and the same limitations apply to the BRIDGE study. Study follow-up was 12 months and does not inform on the long-term use of pegunigalsidase alfa, although patients were able to enrol in the OLE study (F60 study), which is discussed in this report.

Economic Evidence

Economic Evaluation and Budget Impact

- Pegunigalsidase alfa is available as a 2 mg/mL concentrate for solution for IV infusion. At the submitted price of \$706.48 and \$2,825.93 per 2.5 mL and 10 mL single-dose vial, respectively, the annual cost of pegunigalsidase alfa is expected to be \$293,897 per patient, based on the Health Canada–recommended dosage.
- Based on the results of the CDA-AMC base case, pegunigalsidase alfa is predicted to be associated with both higher total costs (compared with agalsidase alfa; incremental costs = \$1,232) and lower total costs (compared with migalastat and agalsidase beta; incremental savings = \$42,488 and \$113,972, respectively), which is entirely driven by costs associated with drug acquisition.
- CDA-AMC estimates that reimbursing pegunigalsidase alfa for the treatment of FD will result in a budgetary saving of approximately \$2 million over the first 3 years of reimbursement compared to the amount currently spent on agalsidase beta, migalastat, and agalsidase alfa, with an estimated expenditure of \$30 million on pegunigalsidase alfa over this period. The actual budget impact of reimbursing pegunigalsidase alfa will depend on the size of the eligible patient population, the distribution of patient weights, the comparator treatments pegunigalsidase alfa captures market share from, and the prices paid by public drug plans for comparator treatments.

CDEC Information

Members of the Committee

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

Meeting date: August 27, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None



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