

CADTH Reimbursement Recommendation

Avalglucosidase Alfa (Nexviazyme)

Indication: For the long-term treatment of patients with late-onset Pompe disease (acid alpha-glucosidase deficiency)

Sponsor: Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.

Final recommendation: Reimburse with conditions

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What Is the CADTH Reimbursement Recommendation for Nexviazyme?

CADTH recommends that Nexviazyme be reimbursed by public drug plans for the long-term treatment of patients with late-onset Pompe disease (LOPD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Nexviazyme should only be covered to treat patients who have a confirmed diagnosis of LOPD, are able to walk, and have never received Myozyme before or were unable to tolerate Myozyme during the first year of treatment. Nexviazyme should not be covered to treat patients who have known Pompe-specific enlargement of the heart muscle, have severe disease, or are unable to perform repeated forced vital capacity (FVC percent predicted) measurements between 30% and 85%.

What Are the Conditions for Reimbursement?

Nexviazyme should only be reimbursed if prescribed by a clinician experienced in treating lysosomal storage diseases or other types of neuromuscular diseases and the price is less costly than Myozyme for the treatment of patients with LOPD.

Why Did CADTH Make This Recommendation?

- One clinical trial demonstrated that Nexviazyme was as good as Myozyme for breathing and walking distance outcomes.
- There was not enough evidence to suggest that Nexviazyme provided any advantage over Myozyme in addressing patients' unmet needs.
- Based on public list prices, Nexviazyme costs less than Myozyme and is considered similarly effective; therefore, Nexviazyme should be priced to be less costly compared to Myozyme.
- Based on public list prices, Nexviazyme is expected to save the public drug plans \$3,041,419 over 3 years.

Additional Information

What Is LOPD?

LOPD is caused by a genetic error that allows complex sugars to build up in the cells of organs and tissues, especially in muscles, causing them to not function properly. Many people with Pompe disease have heart problems and breathing problems, and almost all have muscle weakness. Most patients will have to use wheelchairs and/or oxygen at some point. It is not known how many people in Canada have LOPD. In the Netherlands, the prevalence of LOPD is estimated to be 1 in 57,000 people.

Unmet Needs in LOPD

There is a need for treatments that improve muscle strength and breathing, and prevent disease progression. Patients may also benefit from treatments that are easier to take, have fewer side effects, have a longer duration of treatment effect, and are easier to access without having to travel.

How Much Does Nexviazyme Cost?

Treatment with Nexviazyme is expected to cost approximately \$524,563 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that avalglucosidase alfa be reimbursed for the long-term treatment of patients with LOPD (acid alpha-glucosidase deficiency [GAA]) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multicentre, double-blind, phase III, randomized controlled trial (the COMET study; N = 100) that enrolled treatment-naïve patients with LOPD who were at least 3 years of age, ambulatory, and did not require invasive ventilation, demonstrated that treatment with avalglucosidase alfa resulted in similar clinical benefit as alglucosidase alfa. In the trial, treatment with avalglucosidase alfa was noninferior to alglucosidase alfa, where the mean difference of change in FVC (percent predicted) between treatment groups at week 49 was 2.43% (95% confidence interval [CI], -0.13 to 4.99). Secondary and exploratory outcomes, including the 6-minute walk test (6MWT), were aligned with the noninferiority result observed in the primary outcome of FVC. However, secondary and exploratory outcomes were not controlled for type I error. Patients identified a need for treatments that improve strength and breathing function, and prevent disease progression. Other considerations that patients valued included a better mode of delivery, fewer side effects, a treatment that has a continuous effect in the body, and greater accessibility without the need to travel. There is insufficient evidence to suggest that avalglucosidase alfa provides any advantage over alglucosidase alfa in addressing patients' unmet needs.

Using the sponsor-submitted price for avalglucosidase alfa and publicly listed prices for all other drug costs, avalglucosidase alfa was less costly compared with alglucosidase alfa and considered similarly effective.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with avalglucosidase alfa should be reimbursed when initiated in patients with all the following: <ol style="list-style-type: none"> 1.1. a confirmed diagnosis of late-onset Pompe disease 1.2. are ambulatory 1.3. are treatment naïve or unable to tolerate alglucosidase alfa during the first year after initiating treatment. 	The evidence from the COMET trial supported the efficacy and safety of treatment with avalglucosidase alfa for patients with the outlined clinical criteria. The clinical expert noted to CDEC that intolerance to alglucosidase alfa usually occurs during the first year after initiating treatment.	Diagnosis of Pompe disease should be based on confirmed GAA enzyme deficiency from any tissue source or 2 confirmed GAA gene mutations. Ambulation is defined as the ability to ambulate more than 40 m without stopping and without an assistive device in a clinical assessment setting. Use of an assistive device for community ambulation is allowed.

Reimbursement condition	Reason	Implementation guidance
<p>2. Treatment with avalglucosidase alfa must not be reimbursed when initiated in patients with any of the following:</p> <p>2.1. known Pompe-specific cardiac hypertrophy</p> <p>2.2. severe disease</p> <p>2.3. inability to perform repeated FVC (percent predicted) measurements between 30% and 85%.</p>	<p>There is no evidence to support the efficacy of avalglucosidase alfa in patients with the outlined clinical criteria.</p>	<p>Severe disease can be defined as loss of ambulation or the need for permanent invasive ventilation.</p>
Renewal		
<p>3. Assessment of treatment response should be conducted at 6-month intervals. Treatment with avalglucosidase alfa can be renewed as long as the patient does not meet any of the discontinuation criteria.</p>	<p>This is aligned with clinical practice in Canada based on input by clinical experts.</p>	—
Discontinuation		
<p>4. Treatment with avalglucosidase alfa must be discontinued if the patient develops any of the following:</p> <p>4.1. severe untreatable infusion-related reactions</p> <p>4.2. declining motor or respiratory function at a similar rate as before therapy to the point of loss of ambulation or the need for permanent invasive ventilation.</p>	<p>There is lack of evidence that avalglucosidase alfa would benefit patients who exhibit the outlined clinical presentations. This is aligned with Canadian guidelines for the diagnosis and management of Pompe disease.</p>	<p>Some infusion-related reactions can be managed clinically with pretreatment and desensitization.</p> <p>Loss of ambulation is defined as wheelchair dependent or unable to ambulate 40 m (130 feet) without stopping and without an assistive device; use of assistive device for community ambulation is acceptable.</p>
Prescribing		
<p>5. The patient must be under the care of a clinician experienced in treating lysosomal storage diseases or other types of neuromuscular diseases.</p>	<p>Accurate diagnosis and management of patients with Pompe disease are important to ensure that avalglucosidase alfa is prescribed to appropriate patients.</p>	—
Pricing		
<p>6. The price of avalglucosidase alfa should be negotiated so that it provides cost savings to drug programs relative to the cost of treatment with alglucosidase alfa for the treatment of patients with late-onset Pompe disease.</p>	<p>Based on the submitted list prices, avalglucosidase alfa was cost saving in comparison to alglucosidase alfa.</p>	—

CDEC = Canadian Drug Expert Committee; FVC = forced vital capacity.

Discussion Points

- CDEC discussed that there is a need for new treatments in Pompe disease that improves clinical and health-related quality of life (HRQoL) outcomes over what is currently available. Evidence reviewed by the committee and input from clinical experts suggest that avalglucosidase alfa does not offer any additional clinical benefits over alglucosidase alfa.
- CDEC discussed that based on the few data points and variability after treatment switch from the COMET extension trial at week 97, it is unclear if patients who switched from alglucosidase alfa to avalglucosidase alfa were improving, declining, or maintaining their overall respiratory function, motor function, and HRQoL, and that there is uncertainty in the long-term efficacy of switching treatments. In addition, the committee further discussed that there is no evidence to suggest that patients who are not responding well or experience a plateaued response on alglucosidase alfa would benefit from switching to avalglucosidase alfa.
- CDEC discussed that patients should discontinue treatment with avalglucosidase alfa if they have an estimated short life expectancy either due to advanced stages of decline from Pompe disease or comorbidities.
- It is possible that biosimilars of alglucosidase alfa will enter the market in the future, though at the time of this review, the comparative efficacy or cost-effectiveness of such biosimilars versus avalglucosidase alfa is unknown. CDEC considered there to be a potential risk of avalglucosidase alfa not being cost-effective versus a biosimilar of alglucosidase alfa should such a product enter the market.

Background

Avalglucosidase alfa has a Health Canada indication for the long-term treatment of patients with LOPD (or GAA deficiency). Avalglucosidase alfa is an enzyme replacement therapy. It is available as a dose of 20 mg/kg of body weight by IV infusion every other week and the Health Canada–approved dose is 20 mg/kg of body weight administered every other week.

Pompe disease is a rare, autosomal-recessive disorder caused by pathogenic variants in the GAA gene resulting in dysfunctional GAA enzyme that allows glycogen to accumulate in cells leading to impaired cellular function and tissue damage. Patients with LOPD have variable and reduced enzyme function (between 2% and 40% of normal) while patients with infantile-onset Pompe disease (IOPD) have minimal or no enzyme activity. Pompe disease is diagnosed through molecular testing or enzymatic analysis and the presence of 2 pathogenic variants of the GAA gene confirms a diagnosis. Patients with LOPD do not develop hypertrophic cardiomyopathy (a characteristic of IOPD). Additionally, clinical presentation can be at any age and the rate of disease progression varies among patients. Clinical features can range from a slowly progressive myopathy, which may have been preceded by an asymptomatic interval, to a much more rapid and progressive myopathy that results in wheelchair and ventilatory dependence and early death.

The clinical expert CADTH consulted with for this review estimated that a prevalence of 1 in 40,000 people for all Pompe disease would be reasonable. A study from the Netherlands estimated a prevalence of 1 in 57,000 specifically for LOPD. The incidence of LOPD has been estimated to be 1.75 in 100,000 births. A study using data from births between 1969

and 1996 in British Columbia estimated an incidence of 1 in 115,091 for Pompe disease. It is expected that this is an underestimate of the true number of patients with LOPD in Canada given that many would have been undiagnosed at the time of the study. No updated prevalence or incidence data specific for Canada have been identified.

Clinicians consulted by CADTH for this review indicated that enzyme replacement therapy with alglucosidase alfa, a recombinant human GAA, at a dose of 20 mg/kg by IV infusion every 2 weeks is the standard treatment and the only specific treatment for LOPD, although it is not a cure for Pompe disease. Aside from enzyme replacement therapy, supportive care includes continued monitoring of pulmonary function and motor performance to assess new or increased need for ventilatory support and mobility aids. Other supportive therapies include exercise and dietary changes, while new disease-specific treatments, such as novel forms of enzyme replacement therapy and gene therapies, are in development. Interventions such as physical therapy, occupational therapy, speech therapy, and assistive technological devices can be used to support respiratory and motor function and attempt to improve HRQoL.

Sources of Information Used by the Committee

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

- a review of 1 randomized clinical trial in patients 16 years of age or older with a confirmed GAA enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations
- patients' perspectives gathered by 1 patient group, Muscular Dystrophy Canada, in partnership with the Canadian Association for Pompe
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with Pompe disease
- input from 1 clinician group, including Neuromuscular Disease Network for Canada (NMD4C) and other Pompe disease-treating clinicians
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Muscular Dystrophy Canada, in partnership with the Canadian Association for Pompe, conducted a survey and semi-structured phone or Zoom teleconference interviews with adult patients or the parents and caregivers of children living with Pompe disease. In total, 41 individuals impacted by Pompe disease provided information for the submission.

Respondents frequently reported that Pompe disease negatively impacted motor ability (including mobility, strength, balance, and energy) and breathing. Quality of life was also important to the patient group and the detrimental impacts on social health, mental health, patients' ability to participate in daily activities, and their families were identified as key areas affected by Pompe disease.

Some respondents reported having no experience with medications for Pompe disease and were focusing on physical therapy while others described being on enzyme replacement therapy for years. Of those who have been treated with alglucosidase alfa, some described having minor improvements followed by a plateauing of effect and others felt they had major improvements. Patients and caregivers would like for new treatments to improve strength and breathing function, and prevent disease progression. Other considerations that patients valued included a better mode of delivery, fewer side effects, a treatment that has a continuous effect in the body, and greater accessibility without the need to travel.

Two adults reported having experience with avalglucosidase alfa through a clinical trial and have been receiving the enzyme replacement therapy for 2 to 3 years. During this time, the patients noticed improvements in mobility, balance, and endurance with the most significant benefits being improvements in daily living and mental health.

All patients from the group submission indicated having diagnostic testing performed via blood test and some also had a biopsy to confirm. In general, patients did not have to pay for testing, though there were costs associated with travelling for appointments. Some respondents indicated there were no delays, while others faced multiple tests or significant wait times before receiving a diagnosis, and many patients recalled the stress of being misdiagnosed.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH described the most important goals of currently available forms of treatment being to stabilize and/or improve motor and respiratory function as well as prevent further disease progression. Although reversal of muscle involvement present at the time of diagnosis would be ideal, novel tools to target muscle cell growth and regeneration will need to be developed in the future to achieve this goal. Therapies should also have minimal burden on patients and have a low risk of infusion-related reactions.

The clinical expert expected that avalglucosidase alfa would replace alglucosidase alfa as first-line treatment for Pompe disease and all patients who meet the criteria for treatment would receive the new drug. This would include those who have never received enzyme replacement therapy as well as those already being treated with alglucosidase alfa who would be switched over to avalglucosidase alfa.

Patients with Pompe disease are identified via enzymatic testing and genetic testing. The clinical expert also indicated there is a free multigene panel provided by the drug manufacturer that includes testing for Pompe disease. This has allowed clinicians to screen and identify potential patients before they qualify for the genetic testing that is funded by some jurisdictions.

According to the clinical expert, any patients with symptomatic disease should be treated with enzyme replacement therapy. The heterogeneity of LOPD clinical presentation precludes treatment in the primary prevention setting and patients without symptoms should be closely monitored to detect early signs of disease progression. Patients with very advanced disease, such as those who are wheelchair bound and on permanent invasive ventilation, may be least suited for avalglucosidase alfa, though the clinical expert added that clinical context should be considered on a case-by-case basis.

Canadian evidence-based guidelines for the treatment of LOPD, identified by the clinical expert, emphasize the importance of having and meeting clearly defined, objective outcomes and tracking progression to continue treatment. Assessments for skeletal muscle function (e.g., 6MWT, quantitative muscle strength scoring) and respiratory muscle function (e.g., FVC, maximum inspiratory pressure, maximum expiratory pressure, change in FVC between upright and supine positions) were noted as relevant outcomes in clinical trials. Testing at individual clinics may vary. It is recommended that patients are followed at least annually by a regional centre of excellence. Patients who begin a new therapy should initially be assessed every 6 months, while patients who have been treated long-term and remain stable should be assessed at least annually. For patients who live in remote areas, it may be acceptable to have detailed annual assessments at an expert centre in addition to visits every 6 months with a local physician.

The clinical expert stated that most patients are treated with enzyme replacement therapy until they develop end-stage disease, which could include wheelchair requirements with full-time invasive ventilation. Anaphylactic reaction to the medication that cannot be managed with premedications as well as comorbidities that significantly reduce lifespan (e.g., cancer) may be considerations for discontinuing treatment.

According to the clinical expert, new patients often start their treatment in a hospital clinical setting and, once stable, transition to home infusions. Post-infusion follow-up would always be performed by a centre with expertise in managing patients with Pompe disease.

Clinician Group Input

Clinician input was provided by the Neuromuscular Disease Network for Canada (NMD4C) and 8 clinicians with experience treating Pompe disease.

The clinician group input was similar to that given by the clinical expert consulted by CADTH.

Drug Program Input

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

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions.

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
The product monograph references patients 6 months and older. Would patients who are younger than 6 months be treated with avalglucosidase alfa?	Currently, the use of avalglucosidase alfa in patients younger than 6 months of age is outside the Health Canada–approved indication. CDEC has not reviewed any evidence of the efficacy and safety of avalglucosidase alfa in patients younger than 6 months of age.
Should patients unresponsive to alglucosidase alfa be considered for avalglucosidase alfa therapy?	<p>The clinical expert consulted suggested that patients who may respond when switched from alglucosidase alfa be considered for avalglucosidase alfa.</p> <p>However, based on the results from week 97 of the COMET extension trial, it is unclear if patients who switched from alglucosidase alfa to avalglucosidase alfa were improving, declining, or maintaining their overall respiratory function, motor function, and HRQoL. In addition, there is uncertainty in the long-term efficacy of switching treatments. As such, CDEC recommended that treatment with avalglucosidase alfa not be reimbursed when initiated in patients who previously received alglucosidase alfa except for patients who cannot tolerate alglucosidase alfa within the first year after initiating treatment.</p>
Would treatment with avalglucosidase alfa be lifelong?	Treatment with avalglucosidase alfa is expected to continue until the patient has declined to the point that there is no longer benefit from receiving the drug (e.g., the individual is nonambulatory and has permanent invasive ventilation).
In the recommendation for alglucosidase alfa, the committee recommended that drug plans consult with experts in the management of lysosomal storage disease to develop specific criteria for monitoring and stopping alglucosidase alfa.	CDEC suggests that existing processes and methods for alglucosidase alfa can also be used for avalglucosidase alfa.
Considerations for continuation or renewal of therapy	
Currently listed drugs do not require assessment of response for continued therapy. There are no renewal criteria provided by CADTH for alglucosidase alfa. Should there be renewal criteria for avalglucosidase alfa?	CDEC has outlined renewal and discontinuation criteria in Table 1 of this recommendation.
Considerations for prescribing of therapy	
<p>Who should be able to prescribe avalglucosidase alfa?</p> <p>Should the prescribing criteria for avalglucosidase alfa be aligned with the prescribing criteria for alglucosidase alfa criteria?</p>	Prescription of avalglucosidase alfa should be restricted to those with experience in treating lysosomal storage diseases or other types of neuromuscular diseases. Prescribing criteria for avalglucosidase alfa should be aligned with that for alglucosidase alfa and for LOPD rather than IOPD.

Implementation issues	Response
Generalizability	
<p>Are data available regarding switching from alglucosidase alfa to avalglucosidase alfa?</p>	<p>CDEC noted that data exist for patients who switched from alglucosidase alfa to avalglucosidase. These have been outlined in the clinical report. However, CDEC also noted that there is substantial uncertainty in the presented data that CDEC is unable to determine the efficacy of switching compared to maintaining original therapy.</p>

CDEC = Canadian Drug Expert Committee; HRQoL = health-related quality of life; IOPD = infantile-onset Pompe disease; LOPD = late-onset Pompe disease.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One multicentre, double-blind, active-control, phase III randomized controlled trial was included in the CADTH review for avalglucosidase alfa. The COMET trial was designed to evaluate the efficacy and safety of avalglucosidase alfa 20 mg/kg of body weight given every other week for the treatment of LOPD. The study consisted of a screening period of up to 14 days, a double-blind treatment period of 49 weeks, an open-label extension phase of up to 240 weeks, and follow-up for up to 4 weeks. At the end of the double-blind phase, patients in the alglucosidase alfa treatment group switched treatment to receive avalglucosidase alfa for the duration of the open-label treatment phase. The primary outcome of FVC (percent predicted) in the upright position was used to test the noninferiority of avalglucosidase alfa compared with alglucosidase alfa using a noninferiority margin of -1.1%. Sequential testing continued with superiority testing for FVC (percent predicted) followed by the key secondary outcome of distance walked and percent predicted on the 6MWT. Patients older than 3 years were eligible to participate in the COMET trial if they had confirmed GAA enzyme deficiency from any tissue source and/or 2 confirmed GAA gene mutations. Patients with known Pompe-specific cardiac hypertrophy or who had severe disease (e.g., wheelchair dependent, required invasive ventilation) were excluded from the study. Previous treatment with alglucosidase alfa or other investigational treatments for Pompe disease were also reasons for exclusion.

In total, 100 patients were randomized in a 1:1 ratio to either avalglucosidase alfa or alglucosidase alfa. The mean age of the patients in the COMET trial was 48 years (standard deviation [SD] = 14) and patients were older in the alglucosidase alfa group. Patients were predominantly White (94%), and there was a similar number of male and female patients within and between treatment groups. The baseline mean distance walked on the 6MWT was numerically higher for the avalglucosidase alfa group (399.3 m; SD = 110.9) compared to the alglucosidase alfa group (378.1 m; SD = 116.2). Also, more patients reported using no mobility aids in the avalglucosidase alfa treatment group. Use of a rolling walker and a single crutch were higher in the comparator treatment group (6.1% and 4.1%, respectively) compared to no patients in the avalglucosidase alfa group. The mean age at diagnosis for Pompe disease was lower for patients in the avalglucosidase alfa group (44.73 years; SD = 14.74) versus the alglucosidase alfa group (48.16 years; SD = 14.64). The time between diagnosis and first infusion of study drug was shorter for the avalglucosidase alfa group (15.60 months; SD = 32.06) compared to the alglucosidase alfa group (26.52 months; SD = 59.86).

Efficacy Results

Patients in the modified intention-to-treat population, which was equivalent to the intention-to-treat population, demonstrated a least squares mean (LSM) change in FVC (percent predicted) in the upright position from baseline to week 49 of 2.89% (95% CI, 1.13 to 4.65) for the avalglucosidase alfa treatment group and 0.46% (95% CI, = -1.39 to 2.31) for the alglucosidase alfa treatment group. The mean difference of change between treatment groups was 2.43% (95% CI, = -0.13 to 4.99), for which the lower bound of the 95% CI did not exceed the noninferiority margin of -1.1%, indicating that the criteria for noninferiority of avalglucosidase alfa compared to alglucosidase was demonstrated (P = 0.0074). The P value for superiority testing was not statistically significant (P = 0.0626), thus statistical testing was stopped for all subsequent efficacy outcomes. Analysis of the per-protocol population had similar results with an FVC (percent predicted) LSM change from baseline to week 49 of 2.87% (95% CI, 1.02 to 4.73) and 0.19% (95% CI, -1.83 to 2.21) for the avalglucosidase alfa and alglucosidase alfa groups, respectively. The mean difference of change between treatment groups was 2.69% (95% CI, -0.06 to 5.44; P value for noninferiority = 0.0076 and P value for superiority = 0.0555).

The mean change from baseline to week 49 for the 6MWT distance was 32.21 m (95% CI, 12.47 to 51.94) for the avalglucosidase alfa group and 2.19 m (95% CI, -18.48 to 22.86) for the alglucosidase alfa group. The mean difference of change between treatment groups was 30.01 m (95% CI, 1.33 to 58.69), which was numerically greater for avalglucosidase alfa treatment, with a CI that excluded the null. The mean change from baseline for the 6MWT (percent predicted) was 5.02% (95% CI, 1.95 to 8.09) for the avalglucosidase alfa group and 0.31% (95% CI, -2.90 to 3.52) for the alglucosidase alfa group. The mean difference of change was 4.71% (95% CI, 0.25 to 9.17) between treatments.

Harms Results

During the double-blind phase, 44 patients (86.3%) who received avalglucosidase alfa and 45 patients (91.8%) who received alglucosidase alfa experienced an adverse event (AE). The most frequently reported events were nasopharyngitis (12 patients; 23.5%), back pain (12 patients; 23.5%), and headache (11 patients; 21.6%) for the avalglucosidase alfa group and headache (16 patients; 32.7%), nasopharyngitis (12 patients; 24.5%), and falls (10 patients; 20.4%) for the alglucosidase alfa group. Overall, serious AEs (SAEs) were infrequent among either treatment group. SAEs were reported in 8 (15.7%) patients who received avalglucosidase alfa compared to 12 (24.5%) patients who received alglucosidase alfa. There were 4 patients (8.2%) who withdrew from the alglucosidase alfa group in the study due to the following AEs: acute myocardial infarction, arthritis, dyspnea, and urticaria. No patients withdrew from the avalglucosidase alfa group due to AEs. One death (2%), due to acute myocardial infarction, was reported in the alglucosidase alfa group.

Treatment-emergent anaphylactic reactions (pruritus and rash) were reported for 2 patients (4%) in each of the treatment groups during the double-blind phase. Treatment-emergent hypersensitivity reactions occurred in 12 patients (23.5%) and 15 patients (30.6%) in the avalglucosidase alfa and alglucosidase alfa groups, respectively, with pruritus and rash being the most frequently reported reactions. Treatment-emergent infusion-associated reactions occurred in 13 patients (25.5%) and 16 patients (32.7%) in the avalglucosidase alfa and alglucosidase alfa groups, respectively, with pruritus and nausea being the most frequently reported infusion-associated reactions. Treatment-emergent immune-mediated reactions occurred in █ █ █ who received avalglucosidase alfa and █ █ █ who were treated with alglucosidase alfa, with █ █ █ being the most common. Nearly all patients

were positive for treatment-emergent antidrug antibodies. Overall, 10 patients (21.3%) in the avalglucosidase alfa group and 16 patients (36.4%) in the alglucosidase alfa group had peak titres greater than 12,800. Acute cardiorespiratory failure was not reported in the COMET study.

Critical Appraisal

A key limitation to the COMET trial was the differences in baseline characteristics between the treatment groups. The avalglucosidase alfa group had a younger age at baseline, younger age at diagnosis, shorter time between diagnosis and treatment, greater 6MWT mean distance, and fewer patients who used a mobility aid during the 6MWT. Of note, the time between diagnosis and first infusion of study drug was different between the treatment groups and was not adjusted for in the statistical analysis, which may confound the results. The clinical expert consulted for this review stated that the differences may be a result of the small patient numbers but noted the differences in baseline characteristics in most cases tend to cause biases in the results in favour of the avalglucosidase alfa group. Patients who present at an earlier age are likely progressing at a faster rate and earlier treatment is expected to result in better outcomes, but it is unclear the direction and magnitude of the biases caused by the differences in these factors in the baseline characteristics. All 5 patients (10.2%) who discontinued treatment during the double-blind phase were from the alglucosidase alfa group, and it is unknown what impact these losses had on the results considering the small patient numbers. Nearly all outcomes reported in this review had missing data and methods for handling missing data were lacking, which must be considered when interpreting the results. Missing data were not imputed for the primary outcome and it was assumed that data were missing at random. This assumption may bias 1 treatment over another, though sensitivity analyses were performed to assess the impact of missing data, which supported the missing at-random assumption for the primary outcome. To control for multiplicity, a sequential testing strategy was used, and statistical testing stopped at the first nonsignificant outcome (superiority testing of the primary outcome). As a result, all secondary and tertiary outcomes were not controlled for type I error and should be interpreted as supportive of the primary outcome. Subgroup analyses for the primary outcome were specified a priori, though there was no control for multiplicity, each subgroup had a small number of patients, and the wide 95% CIs indicated imprecision with the estimates.

The noninferiority margin of -1.1% was based on data from the double-blind, placebo-controlled LOTS trial for alglucosidase alfa 20 mg/kg every other week. The noninferiority margin of -1.1% retained approximately half of the lower bound of the 80% CI of the estimated treatment effect of alglucosidase alfa over placebo for FVC (percent predicted) in the LOTS trial at 12 months (i.e., 2.14). The clinical expert believed that this was a reasonable approach to estimate the margin and that it was also a reasonable choice of margin from a clinical perspective. Retaining half of the comparator's treatment effect is consistent with FDA guidance for noninferiority trials. Although FDA guidance indicates that a 95% CI is commonly used, the COMET publication stated that the CI was lowered to 80% at the suggestion of regulatory bodies. The rationale for this was not further described. The constancy assumption is such that the effect of the active comparator (i.e., alglucosidase alfa) in the current noninferiority trial is the same as the effect observed in past trials and requires the trials be sufficiently similar. The similarities in study designs, eligibility criteria, treatment doses, and key outcomes between the COMET and LOTS trials support the constancy assumption. Furthermore, the prespecified constancy assumption analysis estimated an effect of 2.87 for alglucosidase alfa compared to placebo in the COMET trial and an effect of 3.02 in the LOTS trial based on the predictive model. The investigators considered the difference in effect to be

small (-0.15) compared to the noninferiority margin (1.1%). Considering that Pompe disease is rare, the clinical expert noted that the patients who received alglucosidase alfa were mostly similar between the 2 studies. However, key differences in baseline characteristics (e.g., older baseline age, older age at symptom onset, higher FVC, and better 6MWT scores) were noted for patients who received alglucosidase alfa in the COMET trial compared to the LOTS trial. While these differences should bias in favour of alglucosidase alfa treatment in the COMET study, the clinical expert did not feel they explained why the patients in the COMET trial did not respond as well as those in the LOTS trial. Consequently, the lower-than-expected improvements of patients in the alglucosidase alfa treatment group in the COMET study could bias the interpretation of results in favour of treatment with avalglucosidase alfa. While these concerns may impact interpretation of the trend toward superiority noted in the COMET trial, it was the opinion of the clinical expert that the concerns do not impact the statistically significant conclusions of the trial that avalglucosidase alfa was noninferior to alglucosidase alfa.

In general, the patients in the COMET study resembled those seen in clinical practice in Canada. Despite the limited evidence for treatment of pediatric patients with LOPD, the clinical expert consulted for this review stated that the results were generalizable to pediatric patients, but not to patients with IOPD, and highlighted the urgent need for additional data in the IOPD population. The clinical expert noted that clinical practice, background care, and reporting of AEs can vary among countries, which may confound the results. Canadian guidance for the management of patients with Pompe disease suggests regular assessments be performed at least every 6 months, which is less frequent than the study visits in the COMET trial. The greater access to health care resources and attention from clinicians should be considered when generalizing the results to real-world practice. Given that Pompe disease is a lifelong condition, the 1 year of data available for treatment with avalglucosidase alfa during the double-blind phase is somewhat limiting, though the open-label extension phase of the COMET trial is ongoing. The literature search conducted to inform the description and appraisal of outcome measures showed there was a lack of evidence supporting the validity, reliability, or responsiveness to change for some of the trial outcomes. Therefore, there is uncertainty around the use of measures such as maximum expiratory pressure, the Short Form 12-Item (SF-12) Health Survey, and Gross Motor Function Measure-88 (GMFM-88) to assess treatment for patients with LOPD. Furthermore, a literature search did not find any minimal important differences for populations with Pompe disease.

Indirect Comparisons

No indirect treatment evidence for avalglucosidase alfa was identified in this review.

Other Relevant Evidence

NEO1 and NEO-EXT Studies

Description of Studies

The NEO1 study was a phase I, multicentre, open-label, ascending-dose study to determine safety, tolerability, pharmacokinetic parameters, and pharmacodynamic effects of avalglucosidase alfa in patients with LOPD who were treatment naive (group 1) and patients with LOPD who had been previously treated with alglucosidase alfa for at least 9 months (group 2). Patients received IV infusions of avalglucosidase alfa every other week for a total of 13 infusions at 1 of the following doses: 5 mg/kg, 10 mg/kg, and 20 mg/kg. Patients must have been at least 18 years with confirmed GAA enzyme deficiency and/or confirmed

GAA gene mutation, without known cardiac hypertrophy, have a FVC in the upright position of 50% or more predicted, and the ability to ambulate 50 m without stopping and without an assistive device.

The NEO-EXT study is the long-term extension of NEO1. All patients who completed treatment on the 5 mg/kg or 10 mg/kg dose were given the option to enroll in the extension trial and receive the 20 mg/kg dose for up to 6 years. The results summarized in this review focused on the Health Canada–approved 20 mg/kg dose.

Efficacy Results

All efficacy results in the NEO1 study were considered exploratory in nature.

In the NEO1 study, baseline mean FVC (percent predicted) for patients who received avalglucosidase alfa 20 mg/kg were 63.4% (SD = 17.84) and 70.4% (SD = 16.40) in group 1 and group 2, respectively. At week 25, mean FVC (percent predicted) changed to 69.5% (SD = 20.63) and 69.9% (SD = 16.92), in group 1 and group 2, respectively, with a mean change from baseline of 6.2% (SD = 3.15) and 1.4% (SD = 5.71) for the respective groups. In the NEO-EXT study, baseline mean FVC (percent predicted) were 69.2% (SD = 19.27) and 77.3% (SD = 16.45) in the combined group 1 and the combined group 2, respectively. At week 286, mean FVC (percent predicted) changed to 65.7% (SD = 30.07) and 74.5% (SD = 21.24), in the combined group 1 and the combined group 2, respectively. Results beyond week 286 were available; however, reduced patient numbers resulted in uninformative data.

In the NEO1 study, baseline mean 6MWT percent predicted for patients who received avalglucosidase alfa 20 mg/kg were 75.2% (SD = 9.80) and 72.8% (SD = 20.59) in group 1 and group 2, respectively. At week 25, mean 6MWT percent predicted changed to 79.1% (SD = 12.55) and 65.6% (SD = 12.03), in group 1 and group 2, respectively, with a mean change from baseline of 3.9% (SD = 3.45) and -1.3% (SD = 8.94) for the respective groups. In the NEO-EXT study, 6MWT results were 64.9% (SD = 28.05) and 69.1% (SD = 21.37) at week 286, in group 1 and group 2, respectively. Results beyond week 286 were available; however, reduced patient numbers resulted in uninformative data.

Harms Results

In the initial study period of the NEO1 trial, 1 of the 3 patients in group 1 who received the 20 mg/kg dose experienced an AE, namely nasopharyngitis and erythema. All 6 patients in group 2 who received the 20 mg/kg dose experienced an AE, and arthralgia and musculoskeletal pain were the only 2 AEs to be reported in multiple patients (33.3%). In the NEO-EXT trial, all 24 patients, including those who switched to the 20 mg/kg, experienced an AE. The most commonly reported AEs were nasopharyngitis (15 patients; 62.5%), fall (12 patients; 50.0%), diarrhea (11 patients; 45.8%), headache (10 patients; 41.7%), and muscle spasms (10 patients; 41.7%). Of the patients who received the 20 mg/kg dose, none reported an AE in the NEO1 study. In the NEO-EXT study, 9 patients (37.5%) reported a SAE, and there was no individual SAE that was reported in more than 1 individual patient. In the NEO1 study period, no patients who received the 20 mg/kg dose reported an AE that led to treatment discontinuation. In the NEO-EXT study, 1 patient (4.2%) discontinued treatment due to an AE. No deaths due to AE were reported in either the NEO1 or NEO-EXT studies.

Notable harms, including anaphylactic reactions, hypersensitivity, infusion-associated reactions, and immune-mediated reactions, were less common in the NEO1 study period and occurrence increased in the NEO-EXT study. In the NEO-EXT study, 17 patients (70.8%) experienced a treatment-emergent hypersensitivity reaction, 12 patients (50.0%) experienced

a treatment-emergent infusion-associated reaction, 2 patients (8.3%) experienced a treatment-emergent anaphylactic reaction, and no patients experienced a treatment-emergent immune-mediated reaction.

Critical Appraisal

In the NEO1 and NEO-EXT studies, efficacy outcomes were considered strictly exploratory. Inherent to phase I trials are the issues of low number of patients enrolled, lack of a comparator treatment group, and lack of randomization. As a result, it is not possible to determine a causal relationship between the study drug and outcomes observed. The baseline demographics varied between patients receiving different doses, likely due to the low number of patients.

The inclusion of the long-term extension of the phase I NEO1 study in the sponsor’s submission allows for greater generalizability of the safety and tolerability data beyond the time points presented in the pivotal trials; however, the study design greatly limits the generalizability of any findings.

COMET Extension

The long-term results from the COMET extension trial that included data at week 97 indicated that patients who switched treatment from alglucosidase alfa to avalglucosidase alfa after week 49 appeared to show an immediate rise then fall in LSM change from baseline FVC percent predicted with an LSM change from baseline of 0.36% (SE = 1.12%) at week 97. This is compared to the group who received avalglucosidase alfa from study baseline who had an LSM change from baseline of 2.65% (SE = 1.05%) at week 97. Furthermore, patients in the switch group demonstrated fluctuation in LSM change from baseline 6MWT distance after week 49. The switch group had a final LSM change from baseline of 4.56 m (SE = 12.44 m) compared to the group who received avalglucosidase alfa from study baseline who had an LSM change from baseline of 18.60 m (SE = 12.01 m) at week 97. SF-12 physical component and mental component scores did not show a clear trend from week 49 to week 97 for either treatment group. Based on the few data points and variability after treatment switch, it is unclear if patients who switched from alglucosidase alfa to avalglucosidase alfa were improving, declining, or maintaining their overall respiratory function, motor function, and HRQoL. Therefore, there is uncertainty in the long-term efficacy of switching treatments.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Information

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Patients with late-onset Pompe disease
Treatment	Avalglucosidase alfa

Component	Description
Submitted price	Avalglucosidase alfa, 100 mg vial: \$1,596.59
Treatment cost	\$249,752 for a 30 kg patient per year \$624,381 for a 75 kg patient per year
Comparator	Alglucosidase alfa
Perspective	Canadian publicly funded health care payer
Time horizon	1 year
Key data source	COMET trial ^{1,2}
Costs considered	Drug acquisition costs
Submitted results	At an estimated cost of \$524,563 per patient per year, avalglucosidase alfa was \$27,397 less costly than alglucosidase alfa (\$551,960 per patient per year).
Key limitations	<ul style="list-style-type: none"> • The clinical equivalence of avalglucosidase alfa and alglucosidase alfa is uncertain. • There is uncertainty in the mean weight of pediatric patients. • There is uncertainty in the adherence rate.
CADTH reanalysis results	CADTH did not conduct a base-case reanalysis.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The number of patients with LOPD in Canada is uncertain, as is the number who would receive publicly reimbursed treatment.
- Wastage of excess medication and/or rounding doses to the nearest vial was not considered.
- Adherence rates are uncertain.
- The mean weight of the pediatric population is uncertain.

CADTH reanalyses included incorporating wastage by rounding doses to the nearest available vial size.

Based on CADTH reanalyses, the budget impact of reimbursing avalglucosidase alfa for patients with LOPD is expected to be a savings of \$737,680 in year 1; \$1,033,962, in year 2; and \$1,269,777 in year 3, for a 3-year total budgetary savings of \$3,041,419 (or \$3,044,660 when dispensing fees and markups are included) when both new and switching patients are considered. CADTH notes the budget savings are reduced when only new (treatment-naive) patients are considered in the analysis. There is remaining uncertainty in the number of patients with LOPD in Canada who require enzyme replacement therapy.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Initial meeting date: February 24, 2022

Regrets: None

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.

Reconsideration meeting date: June 23, 2022

Regrets: None

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.