Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Sotatercept (Winrevair)

Indication: In combination with standard pulmonary arterial hypertension (PAH) therapy, for the treatment of adults with World Health Organization [WHO] Group 1 PAH and Functional Class (FC) II or III

Sponsor: Merck Canada Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that sotatercept be reimbursed in combination with standard pulmonary arterial hypertension (PAH) therapy, for the treatment of adults with World Health Organization [WHO] Group 1 PAH and Functional Class (FC) II or III only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from a double-blind, placebo-controlled phase 3 randomized trial (STELLAR; N = 323 patients) demonstrated that sotatercept, when added to optimal background therapy, provides significant clinical benefits in patients with symptomatic PAH in WHO FC II or III who were on stable doses of background PAH therapy for at least three months before enrollment. Specifically, compared with placebo, patients treated with sotatercept showed more significant improvement from baseline in the 6-minute walk distance (6MWD) at week 24, with a between-group difference of 40.8 meters (95% CI 27.5 to 54.1). Also, compared those treated with placebo more patients treated with sotatercept met all three composite endpoint criteria (6MWD, NT-proBNP levels, and WHO functional class), with a between-group difference of [redacted]). CDEC noted that a GRADE assessment indicated high-certainty evidence regarding the clinical effectiveness of sotatercept based on these outcomes.

CDEC acknowledged clinicians'- and patients'-identified unmet needs, such as treatments that slow disease progression and improve function and health-related quality of life (HRQoL). CDEC noted that a GRADE assessment of the results from the STELLAR trial indicated a high certainty that compared with placebo, add-on treatment with sotatercept likely improves patients' WHO functional class and reduces PAH-specific hospitalizations, with a moderate certainty of improving HRQoL. Therefore, CDEC concluded that sotatercept met some of the unmet needs identified by patients and clinicians.

Using the sponsor-submitted price for sotatercept and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for sotatercept in addition to optimal background therapy was $436,796 per quality-adjusted life-year (QALY) gained compared with optimal background therapy alone for adult patients with PAH who are not at low risk. The results are driven by the drug acquisition cost, and estimated extension in life and treatment usage (4.3 years). The drug acquisition cost of sotatercept is $199,249 per patient in the first year and $202,155 per patient in subsequent years (based on a weight of 67.5 to 88.9 kg), resulting in a lifetime sotatercept drug acquisition cost of $1,561,624 per patient. As such, price reductions to current optimal background treatment in addition to sotatercept are required for sotatercept to provide optimal value to the public drug plans when added on to optimal background treatment.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Sotatercept should be reimbursed only in patients with confirmed PAH WHO group 1 based on guidelines-approved diagnostic procedure including right heart catheterization	Evidence from the STELLAR trial showed that treatment with sotatercept resulted in benefits in patients with these characteristics.	--
2. Sotatercept must only be reimbursed as add-on therapy in patients who are currently treated with an optimal background therapy for PAH for at least 3 months.	The inclusion criteria in the STELLAR trial states that patients must be on stable doses of background therapy for at least 90 days before screening. Clinical experts were of the opinion that background therapy duration should be between 3 to 6 months.	According to the clinical experts consulted for this review, add-on sotatercept may considered after 3 to 6 months of optimal therapy. Optimal background therapy is defined as "Patients receiving optimal number and doses of therapies according to clinical guidelines". The definition should rely on the latest clinical guidelines developed by organizations of experts in the field of PAH. Clinical variations may exist when defining optimal therapy and should be addressed by treating physicians on a case-by-case basis. For instance, patients may be on double or triple therapy depending on individual contraindications and/or tolerability of available PAH therapies.
3. Sotatercept must be used in patients who are not at low risk.	In the STELLAR trial 83.4% of patients included were categorized as not low risk.	Low risk is defined by COMPERA 2.0 or simplified French Risk Score as: (i) FC I or II and; (ii) 6MWD >440 m; and (iii) NT-proBNP <300 ng/L or BNP <100 ng/L
Renewal		
4. Assessment for clinical response should occur every 12 months	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—
5. For renewal after initial authorization, clinicians must provide proof of beneficial clinical effect, defined as stability or improvement in the patient's risk status when requesting continuation of reimbursement.	In the STELLAR trial 95% of patients treated with sotatercept remained stable or improved in their functional status.	CDEC noted that beneficial clinical effects should be attested by the attending clinician based on professional judgment.
Discontinuation		
6. Patient has undergone lung transplantation.	Patients who previously had a solid organ transplantation were excluded from the STELLAR trial, and Canadian	Patients going into listing for lung transplants can continue being reimbursed until the procedure takes place.

Reimbursement condition	Reason	Implementation guidance
	clinical experts indicated that the treatment should be discontinued in patients who receive a lung transplant.	
Prescribing		
7. Sotatercept should be prescribed by clinicians with expertise in managing PAH.	This is to ensure that sotatercept is prescribed for appropriate patients and that monitoring is optimized and timely.	—
Pricing		
8. A reduction in price	The ICER for sotatercept plus optimal background therapy is $436,796 per QALY gained when compared with optimal background therapy alone. A significant price reduction for sotatercept (>90%), in addition to a 50% price reduction from public list prices for all drugs comprising optimal background therapy, would be required for sotatercept to provide optimal value to the health system.	—
Feasibility of adoption		
9. The economic feasibility of adoption of sotatercept must be addressed	At the submitted price, the incremental budget impact of sotatercept is expected to be greater than $40 million in years 1, 2, and 3.	—

6MWD = six-minute walking distance test; BNP = b-type natriuretic peptide; FC = functional class; ICER = incremental cost-effectiveness ratio; NT-proBNP = N-terminal pro b-type natriuretic peptide; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life year; WHO =World Health Organization

Discussion Points

- The committee noted that sotatercept is indicated to be used as an add-on to "optimal background therapy" and stated that defining optimal background therapy per current clinical guidelines and best practices could help avoid arbitrary variation across settings.
- CDEC also discussed the optimal positioning of sotatercept as an add-on therapy for non-low-risk patients with PAH. The committee noted that sotatercept would be an option in patients who have an absolute contraindication to or who have not tolerated treatment with the components of triple therapy combination or cannot tolerate other drug classes while on a single or dual therapy, or those not meeting treatment targets on dual therapy as an alternative to selexipag when considering escalating to triple therapy.
- CDEC noted the current lack of data to guide the renewal, switching, or discontinuation of the drug based on clinical response. The committee acknowledged the clinical experts' explanation that response to treatment is assessed using multiple factors such as functional class improvements, six-minute walking distance test results, right ventricular function, hemodynamic measurements, overall quality of life, disease stabilization or a slowed disease progression rate. CDEC decided that renewal after initial authorization should be based on beneficial clinical effects attested by the attending clinician based on professional judgment.

- CDEC noted that although the sponsor's long-term study was intended to have a 72-week duration, the follow-up was 45 weeks and 39 weeks in the sotatercept and placebo groups, respectively. The committee decided that the considerably shorter follow-up duration and attritional losses make it challenging to draw a definite conclusion on the long-term benefits of sotatercept.
- The committee discussed the economic evidence for sotatercept and noted that sotatercept plus optimal background therapy was associated with 4.09 incremental QALYs and 4.31 additional life-years at an additional cost of $1,786,879. The incremental cost is driven by direct treatment costs (sotatercept and optimal background therapy), which make up 96% of the total costs associated with treatment with sotatercept plus optimal background therapy. The committee noted that, based on both the sponsor's analysis and CADTH's analysis, there was no price reduction that would allow sotatercept to achieve an ICER of $50,000 per QALY gained. If the prices of all treatments included in optimal background therapy were 50% lower than their public list prices, a price reduction for sotatercept of approximately 95% would be necessary for it to be considered cost-effective at a threshold of $50,000 per QALY gained (reflecting an annual drug cost of $7,970 and $8,086, in the first and subsequent years of treatment with sotatercept). The committee noted the uncertainty associated with the underlying clinical evidence, specifically duration of treatment effect and the use of surrogate outcomes to inform final outcomes, which may result in a higher ICER than that estimated by CADTH.

Background

Pulmonary arterial hypertension (PAH), classified as WHO Group 1 pulmonary hypertension, is a rare, highly progressive, and disabling chronic disease. It is characterized by the uncontrolled proliferation of endothelial and smooth muscle cells in the pulmonary arteries, leading to vascular remodeling, increased pulmonary arterial pressure, and right heart dysfunction. This results in progressive symptoms like dyspnea, fatigue, dizziness, and chest pain, ultimately leading to right heart failure and reduced quality of life and survival. The disease has a complex pathophysiology involving the TGF-β superfamily and is more prevalent in females, with a median diagnosis age of 62.5 years. Despite advances in treatment, PAH has a poor prognosis, with a five-year survival rate of about 56% in Canada. The prevalence of PAH in Canada is estimated at 78 per million population, based on registry data, with considerable variation in global estimates due to different study methodologies.

PAH has non-specific signs and symptoms. The diagnostic process includes cardiac biomarkers like B-type natriuretic peptide (BNP) and NT-proBNP. Echocardiograms can reveal abnormalities in the right ventricular chamber and interventricular septum. The gold standard for diagnosing PAH is right heart catheterization (RHC), an invasive procedure that directly measures pulmonary artery pressure and flow. The current definition of PAH, based on RHC, is a mean pulmonary arterial pressure (mPAP) of >20 mmHg, pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg, and a pulmonary vascular resistance (PVR) of >2.0 WU. Risk status in PAH can be assessed using methods like COMPERA 2.0 or the Simplified French Risk Score. Both methods evaluate three non-invasive parameters: WHO functional class (FC), 6-minute walk distance (6MWD), and BNP/NT-proBNP levels, using the same cutoff values. COMPERA 2.0 assigns grades 1 through 4 to each parameter and calculates the risk status based on the average score. In contrast, the Simplified French Risk Score requires meeting all low-risk criteria to achieve a low-risk status. These parameters are clinically relevant and correlate with long-term survival in PAH patients.

Sotatercept received a Health Canada Notice of compliance (NOC) on August 28th, 2024. Sotatercept is an activin signaling inhibitor for Activin-A and it is available as subcutaneous injection at a recommended dose of 0.3 mg/kg –with a targeted dose of 0.7 mg/kg– administered every three weeks.

Sources of Information Used by the Committee

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

- a review of one pivotal study (randomized controlled trial [RCT]) in adults with PAH and three long-term extension studies,
- patients' perspectives gathered by one patient group: the Pulmonary Hypertension Association (PHA) of Canada,
- input from public drug plans that participate in the CDA-AMC review process,

- three clinical specialists with expertise diagnosing and treating patients with pulmonary arterial hypertension,
- input from one clinician group: The Canadian Pulmonary Hypertension Health-Care Providers,
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

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

Patient Input

CDA-AMC received a submission from the Pulmonary Hypertension Association (PHA) of Canada, which included patient and caregiver survey data and insights. PHA Canada, a charity focused on supporting the pulmonary hypertension community, collaborated with several organizations to gather information on patients' experiences and expectations for sotatercept. The survey found that most respondents were adults with PAH, with idiopathic PAH and scleroderma-associated PAH being the most common subtypes. Diagnosing PAH often takes over two years due to its non-specific symptoms, leading to advanced disease at diagnosis. The disease significantly impacts patients' daily lives and work productivity, with many experiencing severe limitations in physical activities and requiring caregiver assistance.

The socioeconomic burden of PAH is considerable, with many patients underemployed or dependent on assistance. The survey highlighted that current therapies are only somewhat effective in managing symptoms, particularly the psychological and emotional impacts. Adverse effects of medications are common, and patients face barriers to accessing treatments. Patients and caregivers expressed a willingness to tolerate serious adverse effects for benefits such as slowed disease progression, improved quality of life, and better symptom management. Regarding sotatercept, only a few patients reported experience using it, likely through clinical trials, and one patient from the United States shared positive outcomes from the drug's use.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The following input was provided by three clinical specialists with expertise in the diagnosis and management of pulmonary arterial hypertension.

Clinical experts highlighted significant unmet needs in treating pulmonary arterial hypertension (PAH) due to its rarity and lack of curative treatments. Key issues included the heterogeneous drug response among patients, limited options for right heart failure, and scarce guidelines for mixed phenotype PAH or PAH with comorbidities. Additionally, the experts mentioned that there is insufficient data on when to switch or stop treatments based on patient response, and treatment side effects hinder adherence and tolerance.

In terms of the place in therapy, sotatercept, targeting a novel pathway in PAH biology, may show promise in improving outcomes when added to existing therapies, especially for patients whose disease is not well-controlled. The experts mentioned that in the face of scarce evidence, sotatercept should be used as an addition to established treatments rather than a first-line therapy. The novel mechanism could significantly impact patients not meeting treatment goals with current therapies and offer an alternative to chronic infusions. The experts suggested that for new PAH patients who are not high-risk, dual therapy with PDE5 inhibitors and ERAs remains the initial recommendation before considering sotatercept.

Ideal candidates for sotatercept are PAH patients, especially those in group 1 pulmonary hypertension on two to three background therapies without achieving treatment goals. It may also be considered for patients on single therapy if they cannot tolerate other drugs. Patient selection should involve thorough evaluation by PAH specialists, including right heart catheterization, and

consideration for those not reaching low-risk status after standard therapies. Treatment efficacy should be assessed with six-minute walk tests, BNP/NT proBNP levels, and clinical assessments. Assessing the response to treatment should be through functional class improvements, six-minute walk test results, right ventricular function, hemodynamic measurements, and overall quality of life. The clinical experts also considered disease stabilization or a slowed disease progression rate as a meaningful response. Initial treatment response is typically evaluated within four weeks, with a full assessment at three months. If deterioration occurs, earlier reassessment and treatment adjustment may be necessary.

According to the experts, discontinuation should be considered for patients experiencing significant adverse events, like bleeding or telangiectasias, if these significantly impact their quality of life. The decision to discontinue, especially in cases of telangiectasias, should be made on a case-by-case basis, weighing the benefits of continued therapy against the side effects. It should also be stopped if the patient has had a lung transplantation.

The clinical experts emphasized that sotatercept should be managed within specialized PAH centers staffed by trained cardiologists or respirologists. These specialists are essential for diagnosing, treating, and monitoring PAH patients, ensuring comprehensive and high-quality care.

Clinician Group Input

The Canadian Pulmonary Hypertension Health-Care Providers, a non-affiliated group of physicians and nurse practitioners from specialized pulmonary hypertension centers, provided input on the current state and challenges in PAH treatment. Their insights are based on the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines, the 2020 CCS/CTS position statement, recent multicenter Canadian PAH studies, and their collective clinical experience. They emphasized that while current treatment options, ranging from non-pharmacologic management to combination therapy and lung transplantation, offer symptomatic benefits and stability, these are often short-lived. Current PAH medications act mainly as vasodilators and have minimal impact on blocked vessels or the underlying cellular proliferation, leading to disease progression. Despite optimal medical therapy, few patients achieve low-risk status, with a 5-year survival rate of only about 60% in Canada. Key endpoints for Canadian patients include improving symptoms, quality of life, survival, and reducing clinical deterioration.

The clinician group highlighted significant unmet needs in PAH treatment, such as the inability of current therapies to halt or reverse cell proliferation and vessel remodeling. They also noted the intolerable side effects and complications associated with parenteral therapies. They view sotatercept, the first approved PAH therapy targeting growth factor signaling to control aberrant cell proliferation, as a promising add-on therapy rather than a first-line treatment. Sotatercept is expected to benefit patients across common PAH types and major functional classes II and III. The clinician group emphasized the importance of early aggressive treatment in PAH. The group recommends that sotatercept prescribing be restricted to provincially designated pulmonary hypertension (PH) centers.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 2.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
The manufacturer proposes that there are no comparators for sotatercept and notes that all currently available PAH-specific medications in Canada are vasodilators (e.g., phosphodiesterase-5 inhibitors, endothelin receptor antagonists, prostanoids), whereas sotatercept is a novel activin signaling inhibitor that "may reverse the characteristic pulmonary vascular remodeling in PAH." **Comments**:	This is a comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
- It is unclear how many plans currently permit triple therapy for patients with PAH and the proposed reimbursement criteria position sotatercept as part of a triple or quadruple therapy regimen. - It is also unclear how many plans have clearly defined, objective renewal criteria for current PAH therapies.	
Considerations for initiation of therapy	
The manufacturer notes that a confirmative diagnosis of PAH requires an invasive right heart catheterization (RHC) performed by specialists within the PH Centers of Excellence (COEs) located across Canada.	This is a comment from the drug programs to inform CDEC deliberations.
Patients in the pivotal trial were required to be on stable doses of their respective background PAH therapy for at least three months before enrollment and the manufacturer is requesting reimbursement as add-on to "optimal background therapy". **Comment/question:** *If recommended for funding, it will be important to clearly define optimal background therapy.*	Clinical experts described that optimal background therapy is well known and defined among experts in PAH and based in current clinical guidelines. They acknowledged that the optimal number and combination of drugs is used according to the patients' risk status and with the goal to achieve or maintain a low-risk status. Clinical experts emphasized that although optimal background therapy is defined by guideline recommendations, patient tolerance is important, and with the significant side effect profile of some of these drugs, "maximally tolerated optimal medical therapy" can be different than "optimal background therapy".
Considerations for continuation or renewal of therapy	
The manufacturer notes that: - Non-invasive assessments to determine risk status are used for treatment decision-making. - The foundation of modern risk assessment includes exercise capacity, 6-minute walk distance (6MWD) test, WHO FC, and cardiac biomarkers (e.g., N-terminal pro-B-type natriuretic peptide [NT-proBNP]). - Achieving or maintaining a low-risk status is the goal of treatment and is predictive of significantly better long-term survival. **Question**: *-Should there be a minimum response to therapy to justify continuation of the intervention? If so, how should it be defined, both at the first renewal assessment and afterwards?*	Clinical experts acknowledged that achieving or maintaining low-risk status is one of the main goals of treatment and considered that maintaining or improving the patients' risk status would be enough for continuing therapy. The experts recognized that there are no targeted markers to define if and how a patient is responding, and if observing deterioration (an increase) in the patient risk status would suggest considering a discontinuation or to try to escalate therapy. The experts acknowledged that the evidence to establish the best continuation or discontinuation criteria is unclear.
Considerations for prescribing of therapy	
Comment: - It is recommended that hemoglobin and platelet count be reviewed prior to each dose until stable, and then periodically to determine if dose adjustments are required - As noted by the manufacturer, sotatercept should be prescribed under the direction of a specialist in PAH	This is a comment from the drug programs to inform CDEC deliberations.
Generalizability	
Those with a diagnosis of the PAH associated with HIV, portal hypertension, schistosomiasis, and pulmonary veno-occlusive disease were excluded from the pivotal trial. **Question**: *- Should the above patients be excluded from treatment eligibility?*	Clinical experts considered that patients with these conditions should not be excluded from the outset for treatment with sotatercept and rather be considered on a case-by-case analysis to achieve individualized decisions.
System and economic issues	

Implementation issues	Response
Comment: - Comparing to background therapy alone, the BIA predicts that funding of sotatercept in adults with PAH who are not at low risk on optimal background therapy would result in incremental total costs of $38,782,232 in Year 1, $82,425,708 in Year 2, and $115,650,464 in Year 3, for a total incremental costs of $236,858,404 over the three-year projection period.	This is a comment from the drug programs to inform CDEC deliberations.

NA = not applicable; NR = not reported.

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included one pivotal study. The STELLAR trial (NCT04576988), a Phase 3, randomized, multicenter, double-blind, placebo-controlled study, evaluated the efficacy and safety of sotatercept versus placebo on stable background PAH therapy in adults with PAH (WHO Group 1). The trial was conducted across 21 countries, including three sites in Canada, from January 2021 to December 2022, and it enrolled 323 participants with age and gender distributions reflecting typical PAH demographics. The study had two treatment periods: a 24-week Double-Blind Placebo-Controlled (DBPC) phase and a Long-Term Double-Blind (LTDB) phase lasting up to 72 weeks or until unblinding. Participants completing the DBPC phase could join a long-term follow-up study, SOTERIA (NCT04796337). Participants were randomized 1:1 to receive sotatercept or placebo subcutaneously every 21 days, starting at 0.3 mg/kg and increasing to 0.7 mg/kg, with adjustments as needed. The trial included 163 participants in the sotatercept group and 160 in the placebo group, with analyses conducted on the Full Analysis Set (FAS) and Safety Set.

Overall, patients had a mean age of 47.9 years. Almost half of them were in the WHO FC III (166 of 323 randomized [51.4%]) with equal distribution between placebo and sotatercept groups. The rest were classified as WHO FC II. The mean time since diagnosis was 8.8 years for all patients. The study shows no significant differences in the baseline characteristics between study arms.

Efficacy Results

Mortality

In the STELLAR trial, mortality, i.e., the number of patients who died during the follow up of the study, was assessed as part of a multicomponent endpoint (also described below) at the final cutoff date of December 6, 2022. Overall, the number of patients who died were relatively low — less than 4%. More deaths were observed in the placebo arm (6 patients died [3.8%]) than in the sotatercept arm (2 patients [1.2%])

Change from Baseline in 6MWD

Sotatercept significantly improved the 6-minute walk distance (6MWD) in adults with PAH on background therapy, with a median treatment difference between the sotatercept and placebo groups of 40.8 m (95% CI 27.5 to 54.1) at 24 weeks. The improvement was greater in patients within the WHO FC III stratum (61.7 m; 95% CI 40.9 to 82.6) than in those in the WHO FC II stratum (21.7 m; 95%CI 6.6 to 36.7)

Multicomponent Improvement

At Week 24, a higher proportion of patients in the sotatercept group (38.9%) met all criteria for improvement in the multicomponent endpoint (6MWD, NT-proBNP level, and WHO FC) compared to the placebo group (10.1%). The risk difference between groups was [redacted]

Time to Clinical Worsening or Death

By the December 2022 data cutoff, fewer participants in the sotatercept group (11 [6.7%]) than in the placebo group (42 [26.3%]) died or had at least 1 clinical worsening event. The risk difference between groups was [redacted]), this is, a reduction in the

risk of the composite endpoint in favor of sotatercept. Evaluating this composite endpoint as time to event outcome, the risk of death or a first clinical worsening event was 82% lower in the sotatercept group compared with the placebo group (Hazard Ratio [HR]: 0.18; 95% CI: 0.09 to 0.38).

When evaluating the individual components of the composite endpoint, more patients in the placebo arm (17 patients [10.6%]) required rescue therapy or increase in the dose of infusion prostacyclin than in the sotatercept arm (2 patients [1.2%]). PAH-related hospitalization was observed in 7 patients in the placebo arm and one in the sotatercept arm (4.4% vs 0.6%). As mentioned in the mortality outcome section, two patients in the sotatercept arm died compared to six from the placebo arm.

Change from Baseline in PVR

Patients in the sotatercept arm demonstrated a reduction in pulmonary artery resistance (PVR) from baseline to Week 24 of -165.1 dynes*sec/cm-5 (95% CI: -184.0 to -152.0), whereas the PVR increased in the placebo arm by 32.8 dynes*sec/cm-5 (95% CI: 24.0 to 40.0). The median treatment difference between the sotatercept and placebo groups was -234.6 dynes*sec/cm-5 (-288.4 to -180.8). Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis. The treatment effect of sotatercept on PVR at Week 24 was consistent across the pre-specified subgroups and remained consistent in the post-hoc subgroups stratified by baseline risk status.

Change from Baseline in NT-proBNP

The median treatment difference between the sotatercept and placebo groups in mean change from baseline was -441.6 pg/mL (95% CI: -573.5 to -309.6). Results from the supportive analysis using the ANCOVA model were consistent with those from the primary analysis. The treatment effect of sotatercept on NT-proBNP at Week 24 was consistent across the pre-specified subgroups and remained consistent in the post-hoc subgroups stratified by baseline risk status.

WHO FC Improvement

More patients in the sotatercept group (29.4%) showed improvement in WHO functional class at Week 24 compared to the placebo group (13.8%). The risk difference was [redacted]. Specifically, more patients in the sotatercept group than placebo improved from WHO FC II to FC I (5.0% vs 2.0%, respectively), and from WHO FC III to FC II (24.5% vs 12.2%, respectively) at Week 24. The treatment effect of sotatercept on WHO FC improvement at Week 24 was consistent across the post-hoc subgroups stratified by baseline risk status.

Change from Baseline in PAH-SYMPACT Domain Scores

Patients in the sotatercept group reported greater improvements in both the Physical Impacts and the Cardiopulmonary Symptoms domain scores than those in the placebo group from baseline to Week 24. For the Physical Impact domain, the difference between arms was -0.26 points (95% CI: -0.49 to -0.04) in favor of sotatercept. For the Cardiopulmonary Symptoms domain, the values were at -0.13 points (95% CI: -0.26 to -0.01) in favor of sotatercept. In both cases, negative values indicate improvement.

EQ-5D-5L

Sotatercept-treated patients showed a greater increase in the EQ-5D-5L visual analog score (VAS) compared to those on placebo. Specifically, there was an increase (improvement) in the VAS from baseline that was greater in the sotatercept group ([redacted]) than in the placebo group [redacted]). The difference between groups was [redacted] points ([redacted]) in favor of sotatercept.

PAH-specific Hospitalization

Fewer hospitalizations were observed in the sotatercept group compared to the placebo group. This outcome was obtained from the composite endpoint of time to clinical worsening or death. Overall, 7 patients (4.4%) in the placebo group and 1 patient (0.6%) in the sotatercept group were hospitalized, with a risk difference of [redacted] in favor of sotatercept.

Harms Results

Through Week 24, the most common adverse events (AEs) associated with sotatercept when compared to placebo included epistaxis (12.3% vs 1.9% respectively), telangiectasia (10.4% vs 3.1%), and dizziness (10.4% vs 1.9%). These events were mostly mild to moderate in severity. Serious adverse events (SAEs) occurred in 14.1% of participants in the sotatercept group and 22.5% in the placebo group, with no significant patterns emerging. The sotatercept group had isolated instances of atrial flutter, falls, and hemoptysis, with only two SAEs (one fall and one hemoptysis) deemed related to the study intervention. In contrast, the placebo group reported multiple cases of PAH, cardiac arrest, right ventricular failure, and dyspnea. No deaths were reported in the sotatercept group during the initial 24 weeks, compared to six deaths in the placebo group. By the final data cutoff, two deaths occurred in the sotatercept group.

The sotatercept group had a lower discontinuation rate due to AEs compared to the placebo group. Notably, telangiectasia incidents were higher in the sotatercept group but were neither serious nor severe, with only one case leading to treatment discontinuation. The sponsor identified several AEs of special interest, including increased hemoglobin, thrombocytopenia, and various bleeding events. Epistaxis was the most reported bleeding event (12.3%) in the sotatercept group, followed by gingival bleeding (3.1%). None of these bleeding events were serious or severe, though two participants discontinued due to bleeding events. Increased hemoglobin levels were observed in 4.3% of participants in the sotatercept group, leading to study intervention interruption in three cases, but none were serious or severe. Thrombocytopenia was more common in the sotatercept group than the placebo group (6.1% vs. 2.5%).

Critical Appraisal

Internal Validity

The STELLAR trial was a well-designed phase-3, multicenter, double-blind, randomized placebo-controlled study assessing the efficacy and safety of sotatercept versus placebo over 24 weeks in adult PAH patients on stable background therapy. The trial utilized a robust 1:1 random allocation process, generated by a computer algorithm and centrally managed to maintain allocation concealment. Although blinding was effective initially, patients might have inferred their treatment group due to more frequent adverse events like telangiectasia and nosebleeds in the sotatercept group. Adherence was meticulously monitored, with rates exceeding 98%, and deviations were well-documented. Missing data were handled appropriately through sensitivity analyses, which results were in agreement with primary analysis outcomes for key measures like 6MWD, NT-proBNP, PVR, and PAH-SYMPACT. Outcome measurement methods were validated and reliable, and the reported outcomes and analysis plan adhered to the study protocol.

External Validity

The reimbursement criteria for sotatercept target PAH patients on background therapy who do not meet low-risk status – defined by WHO FC I or II, a 6MWD over 440 meters, and specific NT-proBNP or BNP levels.

Overall, the 323 patients in the STELLAR study were deemed representative of the PAH population in Canada, though certain subgroups (e.g., HIV, portal hypertension) and demographics may not be properly represented. The STELLAR study enrolled 53 patients of 323 (16.4%) at low risk, which is an excluded patient population in the suggested reimbursement criteria and 157 patients (48.6%) within the FC II stratum. However, clinical experts consulted by CADTH considered that the impact on the generalizability of results is low and the effects are still applicable to the target population for reimbursement.

The trial's restriction to patients with a baseline pulmonary vascular resistance of at least 400 dyn·sec·cm−5 may not fully represent the broader PAH population. Additionally, the 24-week median treatment duration and study design limit the ability to determine long-term mortality outcomes and extended safety profiles. Although the long term data suggest that efficacy and harm outcomes remain similar to the STELLAR results.

GRADE Summary of Findings and Certainty of the Evidence

GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.[1,2]:

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.

Results of GRADE Assessments

The GRADE assessments included an evaluation of the main outcomes considered important by clinicians, patient groups, and committee members. The comparison evaluated in the GRADE assessments of this report were that of sotatercept against placebo. In Table 3 we present the GRADE summary of findings, respectively, for each comparison.

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:

- Mortality/deaths
- 6MWD
- Multicomponent improvement
- Time to First Occurrence of Clinical Worsening Event or Death
- PVR
- NT-proBNP
- Change in WHO FC
- HRQoL (PAH-SYMPACT® Physical impacts domain score and PAH-SYMPACT® Cardiopulmonary symptoms domain score and EQ-5D-5L
- Hospitalization (PAH specific)
- Harms (AEs, SAEs, AESI)

Table 3: Summary of Findings for Sotatercept Versus Placebo for Patients With PAH

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Sotatercept	Difference (95% CI)		
Clinical Efficacy							
Mortality Follow-up: median 24 weeks	323 (1 RCT)	NA	6/160 (3.8%)	2/163 (1.2%)	[redacted]	Low[a]	Sotatercept may reduce the number of deaths when compared with placebo. The clinical magnitude of the effect is unclear.
6-minute walking distance, change from baseline in meters Follow-up: median 24 weeks	323 (1 RCT)	NA	1.0 (range: -1.0 to 5.0)	34.4 (range: 32.5 to 35.5)	[redacted]	High[b]	Sotatercept results in a clinically important increase in 6-minute walking distance when compared with placebo.
Multicomponent improvement (6MWD and NT proBNP level and WHO FC) Follow-up: median 24 weeks	321 (1 RCT)	NA	16/160 (10.1%)	63/163 (38.9%)	[redacted]	High[c]	Sotatercept results in an important increase in the proportion of patients with multicomponent improvement when compared with placebo.
Composite: time to clinical worsening or death. Follow-up: median 24 weeks	323 (1 RCT)	NA	42/160 (26.3%)	9/163 (5.5%)	[redacted]	High[c]	Sotatercept results in an important reduction in the proportion of patients with the composite endpoint when compared with placebo.
Pulmonary vascular resistance, median change from baseline in dyn.sec.cm^-5 Follow-up: median 24 weeks	323 (1 RCT)	NA	32.8	-165.1 (95%CI: -184.0, -152.0)	[redacted]	High[d]	Sotatercept results in a decrease in pulmonary vascular resistance when compared with placebo. The clinical magnitude of the effect is unclear. [d]
NT-proBNP , Change from baseline in pg/ml. Follow-up: median 24 weeks	323 (1 RCT)	NA	58.6	-230.3 (range: -236.0 to -233.0)	[redacted]	High[d]	Sotatercept results in a decrease in NT-proBNP when compared with placebo. The clinical magnitude of the effect is unclear. [d]
Improvement in WHO FC Follow-up: median 24 weeks	322 (1 RCT)	NA	22/159 (13.8%)	48/163 (29.4%)	[redacted]	High[c]	Sotatercept results in an important increase in the proportion of patients with improvement in WHO FC when compared with placebo.
Hospitalization PAH-specific Follow-up: median 24 weeks	323 (1 RCT)	NA	7/160 (4.4%)	1/163 (0.6%)	[redacted]	High	Sotatercept results in an important decrease in the proportion of patients hospitalized due to PAH when compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Placebo	Sotatercept	Difference (95% CI)		
Health Related Quality of Life							
Health-related quality of life, PAH-SYMPACT and EQ-5D-5L Follow-up: median 24 weeks	(1 RCT)	MD of change from baseline between sotatercept and placebo was -0.26 points (95%CI: -0.49, -0.04) in the PAH-SYMPACT physical domain and of -0.13 (-0.26, -0.01) in the cardiopulmonary symptoms' domain (negative values mean improvement). For the EQ-5D-5L VAS, the MD was [redacted] points more in sotatercept [redacted] higher values mean improvement) in favor of sotatercept. [e]				Moderate[e]	Sotatercept likely results in an important improvement in health-related quality of life measurements (PAH SYMPACT and EQ-5D-5L) when compared with placebo.
Harms							
Adverse events. Follow-up: range 42 weeks to 72 weeks	323 (1 RCT)	NA	149/160 (93.1%)	151/163 (92.6%)	[redacted]	Low[f]	Sotatercept may result in little-to-no clinically meaningful difference in adverse events when compared with placebo.
Serious adverse events Follow-up: range 24 weeks to 72 weeks	323 (1 RCT)	NA	47/160 (29.4%)	40/163 (24.5%)	[redacted]	Low[f]	Sotatercept may result in little-to-no clinically meaningful difference in serious adverse events when compared with placebo.
Adverse events of special interest, Telangiectasia and epistaxis Follow-up: range 24 weeks to 72 weeks	323 (1 RCT)	NA	7/160 (4.4%)	27/163 (16.6%)	[redacted]	High	Sotatercept results in an increase in the proportion of patients with events of telangiectasia or epistaxis when compared with placebo.

Abbreviations: 6MWD = 6-minute walk distance; CI = Confidence interval; EQ-5D-5L = EuroQol 5 Dimensions 5 Level; FC = functional class; MD = mean difference; NA = not applicable; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAH-SYMPACT® = physical impacts domain score of pulmonary arterial hypertension; WHO = World Health Organization.

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.

a. Rated down two levels for imprecision. The 95% CI is wide and may include important effects of benefit but also the possibility of trivial effects. The study presents a low number of events. and it was not powered to detect a difference for this outcome. No MID or threshold of clinical significance was obtained, hence, the null effect was used for determining the target of the rating of certainty.

b. Although the lower limit of the confidence interval (27.5 meters) is below the MID of 33 meters, it was deemed patients and clinicians would consider this an important effect of benefit. Hence, no rating down for imprecision was performed.

c. Clinical experts considered that if 5 to 10 per 1000 patients treated with sotatercept vs placebo improved (or got worse) it would be a meaningful beneficial (or harmful) effect. Hence, no rating down for imprecision was performed.

d. No MID was obtained for this endpoint. Clinical experts considered the lower change observed to be clinically meaningful.

e. MIDs for the Physical Impacts and Cardiopulmonary Symptoms domains were estimated to be -0.3 and -0.2, respectively. Hence, values were rated down one level for imprecision because they include the threshold of the MID. No MID was obtained for the EQ-5D-5L VAS.

f. May be little to no difference between groups, but the 95% CI is wide and includes a possible important reduction in total AEs as well as an increase in AEs, using a threshold of benefit/harm of 20 patients per 1000 treated.

Source: Clinical Study Reports[3,4]

Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

The evaluation of long-term outcomes is supported by three key reports. First, the long-term assessment of adverse events and description of efficacy outcomes of sotatercept were addressed during the Long-Term Double-Blind (LTDB) Treatment Period of the STELLAR trial. Additionally, efficacy and safety endpoints were evaluated in the open-label extension (OLE) phase of the PULSAR phase 2 study. Lastly, the ongoing open-label SOTERIA trial provides primary evidence, though current information is based on interim analyses. Subsequent subsections will provide detailed descriptions of each study.

The primary objective of the STELLAR extension period was to evaluate the long-term incidence of adverse events of sotatercept. After completing the 24-week double-blind, placebo-controlled (DBPC) treatment period, patients entered the long-term double-blind (LTDB) treatment period lasting up to 72 weeks, eventually transitioning to the long-term follow-up (LTFU) study, SOTERIA, upon unblinding. Due to varying enrollment times in STELLAR, some participants had more visits beyond the initial 24 weeks. The PULSAR study, conducted from June 2018 to March 2022, also evaluated the safety and efficacy of sotatercept over a 24-week DBPC period followed by an 18-month open-label extension. SOTERIA, initiated in May 2021 and ongoing across 196 sites in 21 countries, aims to assess the long-term efficacy, safety, and tolerability of sotatercept over up to seven years.

Efficacy Results

STELLAR LTDB Study

The STELLAR LTDB study extended the evaluation of the long-term safety and efficacy of sotatercept beyond the initial 24-week double-blind placebo-controlled (DBPC) phase. As patients transitioned into the SOTERIA study (those who completed the DBPC treatment period and were on treatment in the LTDB treatment period were eligible to participate in the open-label long-term follow-up study), the efficacy outcomes during the LTDB period remained descriptive, maintaining the positive trends seen at Week 24. Sotatercept continued to show superior improvements in 6-minute walk distance (6MWD), pulmonary vascular resistance (PVR), NT-proBNP levels, WHO functional class (FC), and the proportion of participants achieving a low-risk score compared to placebo.

PULSAR Study

The PULSAR study, a phase 2 trial, assessed the long-term efficacy and safety over a 24-week DBPC period followed by an 18-month open-label extension (OLE) phase. Reductions in pulmonary vascular resistance (PVR) were maintained from baseline to months 18 to 24 in both the continued sotatercept group and the placebo-crossed group. Improvements in 6MWD and NT-proBNP levels were also sustained in both groups. The WHO FC improvements were notable, with a high percentage of patients achieving or maintaining FC II and some reaching FC I. Time to clinical worsening events was low and mortality risk scores reflected sustained low-risk status.

SOTERIA Study

The ongoing SOTERIA study, initiated in May 2021, focuses on the long-term efficacy, safety, and tolerability of sotatercept over up to seven years. At one year, patients maintained the improvements in 6MWD, NT-proBNP levels, WHO FC, and low-risk scores consistent with the STELLAR trial results. Clinical worsening events remained low, with only 6.2% of participants in the continued sotatercept arm experiencing such events, and even fewer in the placebo-crossed group. Detailed results will become available as the study progresses.

Harms Results

STELLAR LTDB

The STELLAR LTDB study showed a consistent profile for the harm outcomes in the sotatercept arm compared to the initial 24-week analysis. Common AEs in the sotatercept group included epistaxis, telangiectasia, dizziness, nasal congestion, thrombocytopenia, and increased hemoglobin levels, primarily mild to moderate. The sotatercept group reported two deaths due to AEs, compared to seven deaths in the placebo group. Discontinuation due to AEs was lower in the sotatercept group (3.7%) compared to the placebo group (6.9%).

PULSAR OLE

In the PULSAR OLE phase, all participants in the sotatercept 0.7 mg/kg group reported AEs, similar to those in STELLAR. Serious AEs related to the study drug were reported in 4.8% of participants, including conditions like fever, increased red blood cells, and systemic lupus erythematosus. Discontinuation due to AEs occurred in 19% of participants in the continued sotatercept 0.7 mg/kg arm, with three deaths reported, including one due to a brain abscess. Adverse events of special interest (AESIs) included leukopenia, neutropenia, and thrombocytopenia, occurring in 17.3% of participants. Hemoglobin increases and telangiectasia were noted, with the latter developing after approximately 1.5 years of treatment.

SOTERIA

In the SOTERIA study, 90.8% of participants experienced one or more AEs, with 3.5% discontinuing treatment and 2.8% dying due to AEs. Serious adverse events occurred in 30.3% of patients, with telangiectasia reported in 17.4% of participants, none deemed serious. Epistaxis was the most common bleeding event (22.1%), with serious bleeding events occurring in 5.2% of participants. Increased hemoglobin levels were observed in 14.3% of participants, nonserious, and thrombocytopenia occurred in 6.1%, with three cases being serious and treatment related.

Critical Appraisal

The LTDB phase of the STELLAR study presented efficacy and harm endpoints descriptively due to patient attrition, as participants could transition to the SOTERIA trial. Blinding and randomization were maintained, though unblinding was possible due to adverse events associated with sotatercept. The open-label PULSAR study, lacking a comparator, posed a higher risk of bias, potentially affecting patient expectations and reporting of patientive measures. Similarly, the ongoing SOTERIA study, also open-label and without a comparator, faced similar biases, with potential influences on patient-reported outcomes and the inclusion of patients with good drug performance.

The LTDB phase shared limitations with the pivotal STELLAR trial, particularly the exclusion of patients with certain types of PAH and the inclusion of both WHO FC II and III patients. Extended observation beyond 24 weeks helped confirm adverse events, aligning with pivotal trial results. The PULSAR study included only WHO FC II and III patients, presenting similar limitations. Conducted at 43 centers in eight countries, it lacked Canadian representation, but clinical experts did not express concerns about generalizability from international evidence.

Indirect Comparisons

No indirect treatment comparison was submitted.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the evidence were identified.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with PAH who are not at low risk. Low risk is defined as: • FC I or II AND;

Component	Description
	• 6MWD > 440 m AND; • NT-proBNP < 300 ng/L or BNP < 100 ng/L
Treatment	Sotatercept as an add-on to optimal BGT. Optimal BGT is defined as: • Patients receiving optimal number and doses of therapies according to clinical guidelines. • Patients may be on double or triple therapy depending on contraindications and/or tolerability of available PAH therapies.
Dose regimen	0.3 mg/kg for first dose, followed by 0.7 mg/kg every 3 weeks
Submitted price	Sotatercept 45 mg vial, $8,717.15 Sotatercept 60 mg vial, $11,622.87 Sotatercept 2 x 45 mg vials, $17,434.30 Sotatercept 2 x 60 mg vials, $23,245.73
Submitted treatment cost[a]	First year, per patient annual cost: $152,344 Subsequent years, per patient annual cost: $186,523
Comparator	Optimal BGT includes any combination of the following drugs: • sildenafil citrate and tadalafil (phosphodiesterase-5 inhibitors, PDE5i), • bosentan, ambrisentan, and macitentan (endothelin receptor antagonists, ERA), • epoprostenol, treprostinil, and selexipag, (prostacyclin analogues).
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (30 years)
Key data sources	STELLAR trial COMPERA registry data
Key limitations	• The treatment effect of sotatercept on mortality, hospitalization, and prostacyclin analogue infusion escalation was overestimated in the submitted model. This was a result of double counting the effect of sotatercept on those outcomes by first modeling a reduction in patient risk status (which is associated with the likelihood of these clinical outcomes occurring), and then applying an additional benefit using a hazard ratio for those receiving sotatercept on the same clinical outcomes. There is insufficient evidence to suggest that treatment with sotatercept reduces the risk of mortality, hospitalization, and prostacyclin analogue infusion escalation in addition to the benefit of achieving a lower risk status. • The sponsor assumed that the treatment effect of sotatercept observed from weeks 12-24 in the STELLAR trial would persist indefinitely over a 30-year time horizon, however, the true duration of treatment effect of sotatercept is unknown. • The sponsor estimated mortality in the model based on data from a subgroup of patients from a European PAH registry who had no comorbidities. In Canada, it is anticipated that sotatercept would include patients with PAH who have comorbidities. • In the sponsor's submitted model, 29.6% of patients started in the low-risk health state and were able to receive treatment with sotatercept. However, the target population in this review excluded patients that are low risk.
CADTH reanalysis results	• To account for the identified key limitations, we revised the way in which the treatment effect of sotatercept was included in the model and the population from which all-cause mortality was extrapolated. We were unable to address limitations associated with the duration of treatment effect for sotatercept. • In the CADTH base case, the ICER for sotatercept plus optimal BGT vs. optimal BGT alone was $436,796 per QALY gained (incremental costs: $1,786,879; incremental QALYs: 4.09).

6MWD = 6-minute walk distance; BGT = background therapy; BNP = B-type natriuretic peptide; FC = functional class; ICER = incremental cost-effectiveness ratio; LY = life year; NOC = Notice of Compliance; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; QALY= quality-adjusted life-year.

[a] The weighted average annual cost of sotatercept assumed by the sponsor was calculated based on the patients' weight distribution derived from the STELLAR trial to determine the utilization rates for each kit (45, 60, 2 x 45 or 2 x 60 mg). This distribution indicated that the utilization rates for the 45 mg, 60 mg, 2x45mg and 2x60mg vial kits are 44.73%, 48.38%, 6.88% and 0.01%, respectively.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the definition of optimal background therapy is uncertain, the gradual uptake of treatment with sotatercept is inappropriate, and the uptake of sotatercept is uncertain. Our reanalysis revised the gradual initiation of sotatercept. In the CADTH base case, the 3-year budget impact of reimbursing sotatercept for the requested population is estimated to cost $284,952,390 ($62,051,571 in year 1, $94,650,189 in year 2, and $128,250,629 in year 3). Due to the uncertainty in the eligible population size and market uptake of sotatercept, we conducted scenario analyses to assess the impact of alternative assumptions on the expected budget impact of sotatercept. In these scenarios, the budget impact was sensitive to increases in the eligible population and faster uptake of sotatercept upon its potential listing; the 3-year budget impact of sotatercept increased by 12% and 22%, respectively, in these scenarios.

CDEC Information

Members of the Committee:

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

Meeting date: August 28, 2024

Regrets:

One expert committee member did not attend

Conflicts of interest:

None