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

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

sotatercept (Winrevair)

(Merck Canada Inc.)

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.

April 22, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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Patient Input

PHA Canada

Name of Drug: Sotatercept

Indication: Pulmonary Arterial Hypertension (PAH)

Name of Patient Group: Pulmonary Hypertension Association of Canada (PHA Canada), Pulmonary Arterial Hypertension Foundation of Quebec, Scleroderma Canada, and Scleroderma Quebec

Author of Submission: Jamie Myrah, Executive Director, PHA Canada

1. About Your Patient Group

PHA Canada is a federally registered and accredited charity whose mission is to empower the Canadian pulmonary hypertension (PH) community through support, education, advocacy, awareness, and research. Since 2008, PHA Canada has brought together pulmonary hypertension patients, caregivers, and healthcare professionals to better the lives of all Canadians affected by PH and represent a united national PH community. PHA Canada website

The Pulmonary Arterial Hypertension Foundation of Quebec (HTAPQ) is a provincially registered non-profit founded in 2006. Through support and information, HTAPQ aims to improve the quality of life of people with pulmonary arterial hypertension and their loved ones. HTAPQ website

Scleroderma Canada is a federally registered charity serving the Canadian scleroderma community. Scleroderma Canada is the national advocate for those affected by this rare and difficult disease. Established in 1999, Scleroderma Canada has worked collaboratively with regional and international organizations to bring healthcare research, education, and clinical care together to ensure those affected by scleroderma have access to the latest advances in care. Scleroderma Canada website

Scleroderma Quebec was founded in 1989 by Mr. Gilles Houlé and his wife, Suzanne Houlé and became a federally registered charity in 1992. Scleroderma Quebec provides medical and moral support to patients, information resources for the public and the medical community, and raises funds for scleroderma research. Scleroderma Quebec website

2. Information Gathering

Information for this submission was gathered primarily from two sources:

1. ***Sotatercept Patient Evidence Submission Survey: an online survey of PAH patients and caregivers in Canada conducted in English and French by PHA Canada from March 13 – April 1, 2024***

   This survey aimed to gather feedback from PAH patients and caregivers in Canada about their current treatment experiences and expectations for sotatercept. Two hundred sixteen (216) people completed the study. 82% of respondents were adults diagnosed with PAH, 4% were parents/guardians of children (<18) living with PAH, and 14% were caregivers of adult (>18) PAH patients. Of the patients surveyed, three (3) indicated experience taking sotatercept. Half (50%) of the total responses were from Ontario, 18% from Quebec, and 10% from BC and Alberta. See Table 1 for a complete breakdown of respondents by type and province.

Table 1: Number of responses by type and province, Sotatercept Patient Evidence Submission Survey, 2024

[Object Description: A table with five columns describing the responses received by type and province.]

Residence by Province	PAH Patients >18 years	Caregivers <18 years	Caregivers >18 years	Total Responses
All Provinces	**N=177 (82%)**	**N=8 (4%)**	**N=31 (14%)**	**N=216 (100%)**
British Columbia	17 (10%)	3 (38%)	1 (3%)	21 (10%)
Alberta	19 (11%)	1 (12%)	1 (3%)	21 (10%)
Saskatchewan	2 (1%)	0 (0%)	0 (0%)	2 (1%)
Manitoba	6 (3%)	0 (0%)	0 (0%)	6 (3%)
Ontario	87 (49%)	3 (38%)	17 (55%)	107 (50%)
Quebec	30 (17%)	1 (12%)	8 (26%)	39 (18%)
New Brunswick	7 (4%)	0 (0%)	2 (7%)	9 (4%)
Nova Scotia	3 (2%)	0 (0%)	2 (7%)	5 (2%)
Prince Edward Island	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Newfoundland	6 (3%)	0 (0%)	0 (0%)	6 (3%)
Territories	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Nearly half (46%) of the patient respondents (including those <18 years represented by their parent/guardian) had been diagnosed with PAH for less than five years, as shown in Table 2. The most common PAH subtype reported by patients was idiopathic PAH (46%), followed by scleroderma-associated PAH (26%).

Table 2: Number of years diagnosed with PAH, Sotatercept Patient Evidence Submission Survey, 2024

[Object Description: A table with four columns describing the years diagnosed by adult and pediatric patients.]

Patients by Age	Patients >18 years	Patients <18 years	Total Responses
All Patients	**N=153 (95%)**	**N=8 (5%)**	**N=161 (100%)**

Less than 5 years	70 (46%)	4 (50%)	74 (46%)
Between 5-10 years	47 (31%)	1 (13%)	48 (30%)
More than 10 years	36 (24%)	3 (37%)	39 (24%)

2. ***Socio-Economic Burden of PAH in Canada: an online survey of adult PAH patients in Canada conducted in English and French by PHA Canada and the University of Alberta from August 15 – September 10, 2023***

   This study aimed to evaluate the socioeconomic burden of PAH with an emphasis on workplace- and activity-related limitations, assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire. Most patients who responded to this survey were female (84%) and White (84%), with a mean age of 57. 41% of the responses were from Ontario, followed by 17% from BC and 14% from Alberta. High school was the highest level of education achieved by a third of patients (32%), while two-thirds (65%) had completed some form of post-secondary education. Most patients (84%) self-reported as Functional Class (FC) II or III. See Table 3 for a complete breakdown of respondents by self-reported functional class and province.

   Table 3: Number of responses by functional class (FC) and location, Socio-Economic Burden of PAH in Canada Survey, 2023

   [Object Description: A table with six columns describing the number of responses received by functional class.]

Residence by Province	**FC I (no limitations)**	**FC II (mild limitations)**	**FC III (moderate limitations)**	**FC IV (severe limitations)**	**TOTAL**
All Provinces	**N=18 (8%)**	**N=109 (50%)**	**N=73 (34%)**	**N=17 (8%)**	**N=217 (100%)**
British Columbia	4 (22%)	18 (17%)	12 (16%)	3 (18%)	37 (17%)
Alberta	2 (11%)	16 (15%)	12 (16%)	1 (6%)	31 (14%)
Saskatchewan	0 (0%)	3 (3%)	1 (1%)	1 (6%)	5 (2%)
Manitoba	2 (11%)	3 (3%)	4 (6%)	2 (11.8%)	11 (5%)
Ontario	7 (39%)	51 (47%)	25 (34%)	7 (41.2%)	90 (41%)
Quebec	3 (17%)	7 (6%)	9 (12%)	3 (17.6%)	22 (10%)
Atlantic Region	0 (0%)	11 (10%)	9 (12%)	0 (0.0%)	20 (9%)
Territories	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Information is also drawn from the findings of PHA Canada's 2021 Canadian PH Community Survey and 2013 Burden of Illness Survey. These surveys aimed to measure the physical, social, financial, emotional, and psychological impacts PH patients and caregivers face in Canada. See **Appendix 1**: *The Impact of PH on Canadians, 2021 Canadian PH Community Survey Summary Report* and **Appendix 2**: *The Impact of PH on Canadians, 2013 Burden of Illness Survey Summary Report*. Additional information was obtained from PHA Canada and Scleroderma Canada's joint submission to CADTH in April 2016 regarding the PAH therapy selexipag. Finally, further information is also drawn from personal stories and insights from our collective work supporting PAH patients and their families.

3. Disease Experience

Group 1 pulmonary hypertension—pulmonary arterial hypertension (PAH)— is the rarest type of pulmonary hypertension. PAH occurs when the arteries in the lungs narrow, thicken, and become rigid. The right side of the heart must work harder to push blood to the lungs through those arteries. The extra stress can cause the heart to lose the ability to pump enough blood throughout the lungs to meet the needs of the rest of the body.

There are several subtypes of PAH. PAH may be idiopathic (no known cause) or may develop in association with other medical conditions, including congenital heart disease, liver disease, HIV, and connective tissue diseases such as scleroderma and lupus. PAH can also be associated with particular genes (heritable PAH) or with previous/ongoing use of some drugs, including methamphetamine or certain diet pills.

The most common symptoms of PAH can also be signs of more common medical problems such as asthma, chronic obstructive pulmonary disease (COPD), or heart disease, making diagnosing PAH difficult. In Canada, it is common for it to take more than two years for patients to be accurately diagnosed with PAH, leading to significant delays in access to appropriate care and treatment. Late diagnosis is associated with more advanced disease and poorer prognosis for patients.

Like all forms of PH, PAH has a significant impact on the lives of patients. For scleroderma patients who already experienced significantly low quality of life scores before acquiring PAH, a PAH diagnosis may represent the "end" they have feared since being diagnosed with scleroderma. Amidst the shock and often despair of receiving a diagnosis of a rare, life-threatening condition, patients are also coping with a wide range of physical symptoms associated with PAH, such as:

- Difficulty breathing upon little or no exertion
- Fatigue/loss of energy
- Dizziness upon activity, especially chest constriction (i.e. bending forward) or sudden exertion (i.e. standing up)
- Edema (swelling of legs, feet, and ankles)
- Syncope (loss of consciousness)
- Bluish lips, hands, and feet
- Chest pains

PAH patients surveyed by PHA Canada in 2016 commonly reported difficulty breathing or shortness of breath upon exertion (90% of respondents) and experiencing fatigue (87%). Over 1/3 of patients also experienced other common symptoms, including swelling of the feet/ankles/belly, chest pains, fainting/lightheadedness, heart palpitations, and coughing. The effects of these symptoms included difficulty with climbing stairs (as reported by 86% of patients), doing household chores (79% of patients), walking a short distance (55% of patients), and being intimate with a partner (39% of patients). Many respondents reported limitations to recreation (88%) and travel (74%).

In 2016, over half of patients reported decreased income because of having PAH, with 43% no longer able to work. Similarly, in 2021, 43% of patients agreed that PAH had negatively impacted their ability to earn an income, and 36% were more dependent on income assistance since being diagnosed with PAH. Findings from the 2023 Socioeconomic Burden of Illness study further

demonstrated that PAH patients are frequently underemployed and dependent on financial and daily living assistance. Only 61 (28.1%) patients surveyed were employed, while 151 (69.6%) were not working, and 5 (2.3%) did not specify their work status. As a result of PAH, 61.3% of patients lowered their hours at work, with 44.5% converting from full-time to part-time work (see Table 4). Patients under 65 experienced more frequent changes to work patterns than patients older than 65; conversely, the older population more commonly resigned from work or opted for early retirement. Among working patients, diminished workplace productivity and activity were frequently reported. The mean percentage of work missed due to PAH was 12%, impairment while working due to PAH was 42%, overall work impairment due to PAH was 46%, and activity impairment due to PAH was 54%.

When JN from BC was diagnosed with PAH in 2009, she experienced such severe shortness of breath that she "struggled to get through the day." She could not work at her part-time retail job, which required standing and walking. JN says her breathlessness meant she "couldn't walk from the bed to the closet" without stopping and catching her breath. She could not do basic household chores or participate in leisure activities, such as going for a walk. Similarly, SL from Quebec remarked:

"I have always been an active person; it was hard for me to sit down. Now, I have to space out my activities. If I do too much one day, I pay for it the next. I can still take care of myself, do laundry, go grocery shopping, and take care of the cooking, but I cannot clean my house anymore. I have to have help with that. I am less and less capable of doing activities with my husband. We have a cottage, and it's hard for me to go on the weekends… It's hard to stay positive. It's difficult because you don't know how much longer you have to live."

As the severity of PAH increases, patients become increasingly dependent on caregiver support. As self-reported functional class worsened, the percentage of patients requiring caregiver assistance with daily activities increased, as did the number of hours caregivers lost to caregiving activities, as seen in Table 4 (next page).

Table 4: Caregiver impact by functional class (FC), Socio-Economic Burden of PAH in Canada Survey, 2023

[Object Description: A table with five columns describing impacts on caregivers by functional class.]

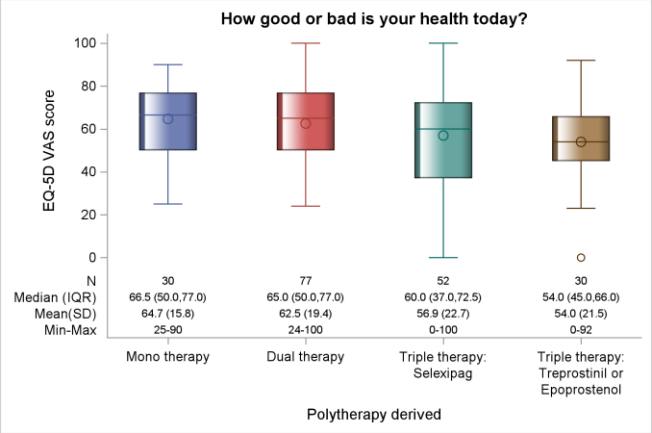
	FC I **(no limitations)**	**FC II** **(mild limitations)**	**FC III** **(moderate limitations)**	**FC IV** **(severe limitations)**
Percentage of **patients requiring assistance** with daily activities	12%	37%	57%	85%
Mean number of caregiver **work hours lost per week** to caring for their loved one with PAH	6	7	10	16

Patients commonly experience depressed mood, anxiety, feelings of helplessness, and hopelessness as they face the realities of living with a serious illness with a high risk of death within a few years. In 2021, 73% of patients reported a lack of understanding of PH among friends and colleagues, and half (53%) felt isolated and excluded from society because PH is not a "visible" disease. A third of patients felt that PH has a bigger negative impact on their lives now than it did when they were first diagnosed, compared to 45% of caregivers. Furthermore, 64 % of patients and 68% of caregivers reported that PH negatively impacts their daily lives.

In the Socioeconomic Burden of Illness study, health-related quality of life on the EQ-5D VAS was similar across age groups and by sex. Still, it decreased with increasing functional class (I to IV) with mean values of 82, 66, 52, and 42, respectively. As expected, PAH patients on triple therapy also reported lower health-related quality of life, as seen in Table 5.

Table 5: Summary of EQ-5D VAS by current PAH therapy, Socio-Economic Burden of PAH in Canada Survey, 2023

[Object description: A boxplot graph showing patient responses to the question “How good or bad is your health today?” with the EQ-5D VAS score ranging from 0 to 100 on the left Y-axis and the polytherapy derived on the X-axis. The graph includes each polytherapy's median, mean, and min-max.]



In 2016, 33% of patients surveyed felt that managing the symptoms or physical impacts of the disease was the most important aspect of PAH to control, and 54% thought it was disease progression. “The progression of the disease – that’s what really scares me,” stated one patient. This was especially true for parent respondents, 100% of whom identified disease progression as the most important aspect of their child’s PAH to control. In 2021, patients (58%) and caregivers (52%) rated improving the overall quality of life as the most important quality in a PH treatment. In 2023, 51% of patients said that preventing PAH from worsening was the most important benefit of a PAH medication, followed by 14% who felt improving symptoms was the most important. In 2024, 90% of patients said it was “very important” that a PAH treatment effectively controls disease progression.

4. Experiences With Currently Available Treatments

There are currently 11 Health Canada-approved therapies available in Canada to treat PAH, including seven oral agents: ambrisentan (Volibris), bosentan (Tracleer), macitentan (Opsumit), sildenafil (Revatio, Viagra), tadalafil (AdCirca, Cialis), riociguat (Adempas), and selexipag (Uptravi), and three infusion therapies: IV epoprostenol (Flolan), IV and SC treprostinil (Remodulin), and IV thermostable epoprostenol (Caripul). There is also one fixed-dose therapy available that combines tadalafil and macitentan (Opsyvni). International treatment guidelines recommend upfront dual oral therapy for most newly diagnosed patients and triple therapy for more advanced patients. For patients with pre-existing and ongoing damage to the vascular system and fibrosis—hallmarks of scleroderma—PAH treatment can be especially complicated with more limited responses to therapies and barriers to accessing infusion therapies in some instances. Specific very rare subtypes of PAH, such as PVOD (pulmonary veno-occlusive disease) and PCH (pulmonary capillary hemangiomatosis), can be uniquely challenging, with lung transplantation currently being the best treatment available. See Table 6 for a breakdown of background PAH therapies according to self-reported functional class as reported in 2023.

Table 6: Summary of current background PAH therapies by functional class (FC), Socio-Economic Burden of PAH in

Canada Survey, 2023

[Object Description: A table with six columns summarizing current background PAH therapies by functional class.]

	FC I (no limitations)	**FC II (mild limitations)**	**FC III (moderate limitations)**	**FC IV (severe limitations)**	**TOTAL**
Background therapy	**N=18 (8%)**	**N=109 (50%)**	**N=73 (34%)**	**N=17 (8%)**	**N=217 (100%)**
No PAH therapy	6 (33%)	12 (12%)	7 (10%)	3 (18%)	29 (13%)
Mono therapy (oral)	2 (11%)	21 (19%)	7 (10%)	0 (0%)	30 (14%)
Dual therapy (oral)	3 (17%)	42 (39%)	12 (16%)	5 (29%)	62 (29%)
Dual therapy (infusion)	0 (0%)	5 (5%)	8 (11%)	2 (12%)	15 (7%)
Triple therapy (oral)	7 (39%)	16 (15%)	24 (33%)	5* (29%)	52 (24%)
Triple therapy (infusion)	0 (0%)	12 (11%)	15 (21%)	3 (18%)	30 (14%)

*one patient indicated two medications of the same type (oral and infusion), possibly due to a transition between medications

In 2016, before the availability of selexiapg (Uptravi), the majority of patients were on dual therapy, and approximately 30% of respondents were on some form of infusion (IV or subcutaneous) therapy. In 2023, the number of patients on infusion-based therapies decreased to 21%, while another quarter (24%) reported being on triple oral therapy using selexipag. By comparison, in 2024's survey, 16% of patients reported being on an oral prostacyclin therapy (selexipag) versus 16% who reported being on an infusion-based therapy (epoprostenol or treprostinil).

Like in 2016, patient experience with PAH treatment is generally positive, with most patients reporting at least some benefit from their current therapies. However, this experience varies considerably by the patient and depends on the symptom in question. For instance, 58% of patients surveyed in 2024 (including parents of pediatric patients) found their current therapy was only "somewhat effective" at controlling shortness of breath upon exertion, compared to 17% who found it to be "highly effective." Patients were most likely to report that their current therapy was "highly effective" at controlling shortness of breath at rest (50%), chest pains at rest (46%), chest pains upon exertion (31%), fainting (31%), and coughing (25%). They were most likely to report that their current therapy was "not effective" at controlling the psychological/emotional impacts of the disease – i.e., depression (35%), fatigue or tiredness (28%), or the physical impacts of disease – i.e., limitations to day-to-day activities (21%). Patients were more likely than in 2024 to believe that their current treatment was "somewhat effective" at controlling disease progression; however, they were also more likely not to know if their treatment was effective at controlling for this critical factor – see Table 7. Meanwhile, 91% of patients in 2024 reported that controlling for disease progression was "very important," second only to controlling for shortness of breath upon exertion (92%).

Table 7: Effectiveness of current treatments at controlling disease progression, Selexipag Patient Evidence Submission Survey, 2016 vs. Sotatercept Patient Evidence Submission Survey, 2024

[Object Description: A table with five columns comparing patient attitudes about the effectiveness of current PAH therapies in 2016

and 2024.]

	Highly Effective	Somewhat Effective	Not Effective	Do Not Know
Patient responses – 2016	25%	35%	22%	18%
Patient responses - 2024	24%	43%	7%	26%

Patients are also managing the adverse effects of currently approved medications, which commonly include nausea, gastrointestinal distress, fatigue, sleeping difficulties, headaches/body pain, and flushing. The side effects most frequently cited by the PAH patients are like those reported by patients in 2016 – see Table 8. The percentage of patients reporting pain or infection at their infusion site has also remained steady at 14%.

Table 8: Most common treatment side effects, Selexipag Patient Evidence Submission Survey, 2016 vs. Sotatercept Patient Evidence Submission Survey, 2024

[Object Description: A table with six columns comparing the most common treatment side effects reported by patients in 2016 and 2024.]

	Headaches & Body Pain	Sleep Difficulties	Flushing of the Skin	Digestive Problems	Stuff/Runny Nose
Patient responses – 2016	52%	44%	33%	45%	42%
Patient responses - 2024	56%	49%	48%	47%	45%

Barriers to accessing treatments also exist. Nearly a third of patients surveyed in 2024 (29%) reported relying on a drug manufacturer's compassionate access program to access their prescribed PAH-targeted therapy. Another 20% were unable to tolerate their PAH-targeted medication due to adverse effects. 12% reported paying out of pocket for treatment, and 6% reported paying out of pocket for supplies. Not surprisingly, patients with more advanced disease progression spend more money travelling to the doctor/hospital and on parking and professional caregiving services – see Table 9 (next page).

Table 9: PAH-related expenses paid by patients per year by functional class (FC), Socio-Economic Burden of PAH in Canada Survey, 2023

[Object Description: A table with six columns describing annual PAH-related expenses patients pay according to their functional class.]

	FC I	FC II	FC III	FC IV	TOTAL

	(no limitations)	(mild limitations)	(moderate limitations)	(severe limitations)	
Annual PAH-related expenses	**N=18 (8%)**	**N=109 (50%)**	**N=73 (34%)**	**N=17 (8%)**	**N=217 (100%)**
Travel to doctor, hospital, and health visits	$375	$390	$363	$747	$396
Parking fees at a pharmacy, hospital, or health-related visit	$60	$78	$93	$140	$86
Professional Caregivers	Nil	$341	$357	$1,429	$401

"It's a good thing I switched to public health insurance when I did. Otherwise, I would never have been able to afford my PAH medications. 20% of $5,000/month [on private insurance] would have been unaffordable."

5. Improved Outcomes

PAH patients and caregivers share high expectations for sotatercept, particularly its potential to slow disease progression and possibly be the first disease-modifying treatment for PAH. Patients had the highest expectations for improving patient quality of life (68% of respondents), slowing disease progression (64%), and improving symptom management (58%). Caregivers of pediatric and adult patients had the highest expectations for improving patient quality of life (80% of respondents), slowing disease progression (77%, including 100% of parents/guardians of children with PAH), and increasing symptom management (77%).

These expectations align with the top three benefits patients are willing to tolerate serious adverse effects for, which are also slowed disease progression (82% of respondents), increased quality of life for patients (79%), and improved symptom management (62%). This was very similar for caregivers of both pediatric and adult patients, whose top three benefits worth tolerating serious adverse effects were also slowed disease progression (87% of respondents, including 100% of pediatric caregivers), increased quality of life for patients (77%), and improved symptom management (67%). A small minority of respondents—seven (7) in total— expressed no willingness to tolerate adverse effects.

I cannot emphasize enough how important this new medication is to this community. I'm on triple therapy now, and my next move will likely be a transplant. Not only is a double-lung transplant risky and life-changing, but it's also very, very expensive to the health system, both in the short-term and with the long-term maintenance and complications that accompany it. Sotatercept is the first drug out there with the potential to reverse the disease process, give us our lives back, and allow us to be active, contributing members of society. If funding this drug helps to avoid or even delay transplants, it will have paid for itself in the long term. More than that, it could very well be the only way to keep me healthy, keep me working, and keep me able to parent my kids. Who knows? Maybe I'll even get to see grandkids one day. Please, we need this. We need this hope.

6. Experience With Drug Under Review

There are very few patients in Canada who have experience with sotatercept. Patients in Canada base their expectations on the results of global clinical trials, the optimism of their medical providers, and the experiences of patients in the US. Overall, patients are optimistic that sotatercept will provide a disease-modifying treatment option that is easier and more tolerable than the current standard of care.

Three people responded to the sotatercept survey indicating experience taking the drug sotatercept. These patients could only have accessed sotatercept through the clinical trial in Canada, which means they would have been receiving background therapy of mono, dual, or triple PAH-targeted treatment. PHA Canada did not speak directly to these patients to verify their experiences in the sotatercept trial. Currently, the principal investigators in Canada report not knowing yet which patients received the drug and which received a placebo during the trial. Therefore, it cannot be verified that the patients reporting experience with sotatercept have received sotatercept, as they could have received a placebo.

These patients report high variability in their experience of sotatercept. All three reported no changes to their shortness of breath at rest (the only experience shared by all three respondents). Shortness of breath upon exertion was unchanged for one patient, worsened for one, and one patient was unsure. Tiredness and fatigue also varied, with one patient reporting a change, one reporting no change, and one reporting worsening symptoms. There were also single reports of the following symptoms worsening: swelling of the abdomen, chest pain upon exertion, lightheadedness, and heart palpitations. None of the patients reported any pain or swelling at their injection site or any bleeding, a more severe side effect that can be associated with sotatercept.

Two of the three patients were unsure if sotatercept was more effective than current therapies in slowing disease progression, and the third reported the same effectiveness as current treatments. Two of the three also agreed that sotatercept offered the same efficacy in addressing the physical and social limitations of the disease.

The only thing all three patients agreed on was that sotatercept was easy to use. Injection of sotatercept every three weeks makes it a considerably more manageable therapy than any other PAH therapy currently available in Canada, especially infusion-based therapies, which are invasive, time-consuming, and have severe and unpleasant side effects. Infusion-based therapies require a high degree of support. They may not be suitable for patients who live without a caregiver or with co-morbidities such as connective tissue disease (i.e., scleroderma), addiction (i.e., methamphetamines), or cognitive impairment.

In comparison to the survey respondents, an American patient who is on the open-label extension trial for sotatercept has been publicly sharing their experience taking the drug at home. This is how they describe their experience:

“I take the drug once every 21 days by subcutaneous injection. Currently, I get a 9-week supply at the clinic, which is three injections, and my fourth is in the clinic to pick up the next round. I am required to take a pregnancy test before injection. I mix the meds at home like I do for my other PAH meds. The side effects I’ve had are nosebleeds and high hemoglobin…. It's given me exceptionally great results and has been so hope-filling. My BNP [biomarkers of heart failure] went from 168 in September 2021 to 11 in April 2023. My right ventricular pressure went from 120 in November 2021 to 63 in May 2023. Those are real numbers. I now have a normal-looking heart, and both sides are normal, which has never happened before.”

Quotes provided by GL, PAH patient on triple therapy, including subcutaneous treprostinil (Remodulin), Florida, USA

7. Companion Diagnostic Test

Not applicable

8. Anything Else?

Not applicable

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

The contributing partner organizations assisted in distributing the patient/caregiver survey and provided feedback on the submission.

Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

Data analysis from the Socioeconomic Burden of Illness study was provided by the Canadian VIGOUR Centre at the University of Alberta.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have a direct or indirect interest in the drug under review.

Table 1A – Financial Disclosures for PHA Canada
Table 1B – Financial Disclosures for HTAPQ [Note, no payments to disclose]
Table 1C – Financial Disclosures for Scleroderma Canada
Table 1D – Financial Disclosures for Scleroderma Quebec

Table 1A: Financial Disclosures – PHA Canada

Check the Appropriate Dollar Range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck (direct)				X
Bayer (indirect)			X	
Janssen (indirect)				X
United Therapeutics (indirect)				X

Table 1B: Financial Disclosures – HTAPQ (N/A)

Check the Appropriate Dollar Range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000

nil				
nil				

Table 1C: Financial Disclosures – Scleroderma Canada

Check the Appropriate Dollar Range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck (direct)			X	
Janssen (indirect)			X	

Table 1D: Financial Disclosures – Scleroderma Quebec

Check the Appropriate Dollar Range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck (direct)			X	
Janssen (indirect)			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jamie Myrah

Position: Executive Director

Patient Group: PHA Canada

Date: April 22, 2024

<Copy and paste here>

Clinician Input

Canadian pulmonary hypertension health-care providers

CADTH Project Number: SR0828-000

Generic Drug Name (Brand Name): sotatercept (WINREVAIR)

Indication: Pulmonary Arterial Hypertension

Name of Clinician Group: Canadian pulmonary hypertension health-care providers

Author of Submission: First draft by Jason Weatherald and David Langleben. All clinicians below contributed

1. About Your Clinician Group

We are a non-affiliated group of physicians and nurse practitioners from provincial specialized pulmonary hypertension centres. The treatment of patients with pulmonary arterial hypertension (PAH) is highly centralized in these expert referral centres in Canada. The purpose of this letter is to request rapid approval and reimbursement of sotatercept for patients with PAH.

2. Information Gathering

The information in this submission is primarily derived from the recent 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) pulmonary hypertension guidelines[1], which is the most recent and rigorous international guideline, and the 2020 Canadian Cardiovascular Society/Canadian Thoracic Society (CCS/CTS) position statement on pulmonary hypertension[3]. We also include published evidence from recent multicentre Canadian PAH studies[3,4] and our collective perspectives based on clinical experience and knowledge of patient outcomes and access to therapies in the Canadian context.

[1]Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023 Jan 6;61(1):2200879. doi: 10.1183/13993003.00879-2022. PMID: 36028254.

[2]Hirani N, et al. Canadian Cardiovascular Society/Canadian Thoracic Society Position Statement on Pulmonary Hypertension. Can J Cardiol. 2020 Jul;36(7):977-992. doi: 10.1016/j.cjca.2019.11.041. PMID: 32682511.

[3]Zelt JGE, et al. Mortality trends in pulmonary arterial hypertension in Canada: a temporal analysis of survival per ESC/ERS guideline era. Eur Respir J. 2022 Jun 2;59(6):2101552. doi: 10.1183/13993003.01552-2021. PMID: 34675044; PMCID: PMC9160389.

[4]Ostad S, et al. Association Between the Pulmonary Artery Pulsatility Index and Prognosis in Pulmonary Arterial Hypertension: A Multicentre Study. CJC Open. 2023 Apr 25;5(7):545-553. doi: 10.1016/j.cjco.2023.04.005. PMID: 37496788; PMCID: PMC10366663.

3. Current Treatments and Treatment Goals

The current treatment paradigm in Canada largely reflects the recommendations of the ESC/ERS 2022 guidelines and the 2020 CCS/CTS Position Statement, consisting of a regular multiparametric risk-based approach to treatment selection and treatment escalation. The European guidelines provide an updated and more nuanced guidance to risk stratification than is outlined in the 2020 Canadian position statement and also include the consideration of cardiopulmonary comorbid conditions in treatment decisions.

The non-pharmacologic management options for PAH treatment include psychosocial support, education, vaccination, and recommendation of avoiding pregnancy in females of childbearing age. Supervised exercise-based rehabilitation is also effective and recommended for patients after being stabilized on PAH therapies, though access to such programs varies widely across Canada. For most newly diagnosed patients with PAH who are at low or intermediate risk, initial combination therapy with a phosphodiesterase type-5 inhibitor (PDE5i) and an endothelin receptor antagonist (ERA) is recommended. In high-risk patients, a more aggressive strategy of intravenous epoprostenol or subcutaneous Treprostinil infusions is recommended, usually in combination with a PDE5i or ERA where this strategy is tolerated and possible based on reimbursement criteria as this approach has been associated with better outcomes in non-randomized studies[5]. Not all patients are able or willing to receive parenteral therapies due to their complexities of administration and often challenging side effect profiles. For patients on oral therapies with PDE5i and

ERA who are not achieving a low-risk status or who are clinically worsening, the options include the addition of an oral prostacyclin receptor agonist (selexipag), escalation to a parenteral therapy (intravenous epoprostenol or subcutaneous Treprostinil), or switching the PDE5i to a cyclic soluble guanylate cyclase stimulator (riociguat). An extremely small proportion of PAH patients have an 'acute vasoreactive response' to inhaled nitric oxide at the time of diagnosis of PAH, and this group can be treated with high dose calcium channel blockers (eg. Nifedipine, amlodipine). Many patients also require oxygen for hypoxemia, diuretics for symptoms of right heart failure and venous congestion (e.g. ascites or peripheral edema). Anticoagulation is sometimes added in patients with idiopathic or heritable PAH but this is less frequently used now than in the past and has conflicting data to support its use. In some centres, anticoagulation is used for any patients with central venous catheters (for epoprostenol infusion) to prevent catheter related thrombosis.

The current PAH medications provide some symptomatic benefit and stability to the patients, but it is often short-lived. They function mainly as vasodilators of less diseased blood vessels, but have minimal effect on the blocked vessels or the cellular proliferation that leads to disease progression. The existing PAH therapies have not been shown to have disease-reversing or disease-modifying effects. Even with optimal medical therapy, only a minority of patients with PAH achieve the treatment goal of obtaining a low-risk status. A recent analysis showed that 5 year survival for PAH was only approximately 60% in our Canadian population. The hospitalizations required during deterioration represent a significant health care system cost and are associated with high risk of future mortality. Most patients ultimately die from complications of PAH such as right heart failure. Some patients require life-saving lung transplantation, though this is an invasive, costly and complicated intervention, and not all patients with PAH are eligible for transplantation.

The most important endpoints for patients in a Canadian study were to improve symptoms and quality of life, prolong survival, and reducing the risk of clinical deterioration (including delaying or preventing hospitalizations or transplantation)[6]. Among the top 10 priorities for future research identified in a Canadian study of PAH patients, their caregivers and clinicians, was to identify ways that PAH can be reversed or put into remission with disease modifying therapies[7].

[5]Boucly A, et al. Association between Initial Treatment Strategy and Long-Term Survival in Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2021 Oct 1;204(7):842-854. doi: 10.1164/rccm.202009-3698OC. PMID: 34185620.

[6]Mai V, et al. Patients' perceptions on clinical trials outcomes in pulmonary arterial hypertension therapy. Thorax. 2023 Jul;78(7):721-725. doi: 10.1136/thorax-2022-219490. Epub 2023 May 4. PMID: 37142420.

[7]Weatherald J, et al. Priorities for pulmonary hypertension research: A James Lind Alliance priority setting partnership. J Heart Lung Transplant. 2023 Jan;42(1):1-6. doi: 10.1016/j.healun.2022.09.015. Epub 2022 Oct 3. PMID: 36283952.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

As is described above, only a minority of patients achieve low risk status with any and all of our current therapies. For all others, the survival curve is steeply downhill. Even patients with initial seeming success may later deteriorate. This is likely because our current therapies do not halt or reverse cell proliferation and remodelling of obstructed pulmonary microvessels. For many patients, the medications have intolerable side effects, limiting the use of maximal therapy in each patient. These may include significant headache, flushing, rashes, nasal congestion, bony and jaw pain, diarrhea, and others, The parenteral therapies require constant attention and there are risks of infection, thrombosis, and interruption of the infusion. Many patients refuse to be constantly attached to a pump.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Sotatercept is the first approved PAH therapy that acts by altering growth factor-signalling that controls the aberrant cell proliferation in PAH, whereas all of our currently available therapies act principally as vasodilators. Sotatercept has been in clinical trials as an add-on therapy in combination with the currently available vasodilator therapies. The effects are complementary in that, when effective, the vasodilators rapidly improve the reduced cardiac output seen in in PAH, thereby reducing deterioration while the

sotatercept takes effect over several months and reduces the pulmonary artery pressure. Based on the available data sotatercept is not expected to be used as a first line treatment. There are other ongoing trials evaluating the efficacy of sotatercept in recently diagnosed patients with PAH but those results are not yet available. The STELLAR trial showed that sotatercept offered benefit over a range of disease severity, functional classes and types of PAH. The FDA gave sotatercept a broad general approval for use in PAH, without specifying subgroups or insisting on late initiation.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

PAH is fundamentally a disease of abnormal cell proliferation in the pulmonary microvasculature which chokes off the blood circulation from inside. Because of its mechanism of action on cell proliferation, sotatercept offers benefit to patients with all common types of PAH, and in the major functional classes II and III. Like an aggressive cancer, PAH should be attacked as early as possible in the patient's presentation. The patients are carefully screened and followed in university hospital based PH specialty clinics across Canada and, in most all cases prescribing is restricted by the provinces to those centers. This results in controlled appropriate use, with guideline-based quality diagnosis prior to therapy, and guideline-based followup. The centers ensure that proper diagnosis of PAH with right heart catheterization and comprehensive evaluations is made, so there is no misdiagnosis.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The clinical trials for PAH principally examine changes in hemodynamics, functional capacity, symptoms, clinical deterioration, and measures of right heart stress, such as NT-BNP and echocardiogram. These parameters are precisely those used for risk prognostication, and they are routinely and regularly evaluated in the PH centers during clinic visits, for purposes of risk stratification.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Thus far, we have not had to discontinue anyone. Dose adjustments are required for thrombocytopenia and polycythemia, but these are manageable by following a dosing algorithm. There is a slight increase in bleeding risk (mainly GI) but this has so far not necessitated stopping the medication.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Suggest restrict prescribing to provincially designated PH centers only

6. Additional Information

None

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Jason Weatherald, MD

Position: Respirologist, Associate Professor, University of Alberta

Date: <11-04-2024>

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck**			X	
Janssen		X		

* Place an X in the appropriate dollar range cells for each company.

**I declare that I was a consultant to Merck for this specific CADTH submission.

Declaration for Clinician 2

Name: Nathan Hambly, MD

Position: Respirologist, Associate Professor, McMaster University

Date: 11-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck		X		
Janssen		X		
Boehringer Ingelheim			X	
Astra Zeneca	X			
Roche		X		
GSK	X			

* Place an X in the appropriate dollar range cells for each company.

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: John Swiston

Position: Associate Professor, UBC

Date: 11-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
J&J Janssen		X		
Merck		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: David Christiansen

Position: Assistant Professor, Rady Faculty of Medicine, University of Manitoba

Date: 12-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen/Actelion	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Sanjay Mehta

Position: Professor of Medicine, Western University, London, Ontario

Date: 12-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen Pharmaceuticals		X		
Merck Pharmaceuticals	X			
Acceleron Pharmaceuticals		X		
Pulmovant/Roivant	X			
Natco Pharma	X			
SpecialtyRx Pharmacy			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Karen Laframboise

Position: Respirologist, Associate Professor of Medicine, University of Saskatchewan

Date: 12-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
NONE				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Paul Hernandez

Position: Respirologist, QEII Health Sciences Centre, Nova Scotia Health; Professor of Medicine, Dalhousie University

Date: 14-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen		X		
Merck		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Doug Helmersen, MD

Position: Respirologist, Clinical Associate Professor, University of Calgary

Date: 14-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen				X
Merck			X	
United Therapeutics			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: David Langleben

Position: Professor of Medicine, McGill University

Date: 12-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen		X		
Merck			X	
Aerovate	X			
Enzyvant		X		
PhaseBio		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: John Thenganatt

Position: Respirologist, Toronto General Hospital

Date: 14-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Steeve Provencher, MD

Position: Professor of Medicine, Université Laval

Date: 12-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 11: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Janssen		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Dr Stephen Archer

Position: Director of the Translational Institute of Medicine

Date: 12-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 12: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 13

Name: Kristina Kemp

Position: Respirologist, Assistant Professor, Dalhousie University

Date: 16-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 13: Conflict of Interest Declaration for Clinician 13

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck		X		
Janssen			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 14

Name: Mitesh Thakrar

Position: Clinical Associate Professor, University of Calgary

Date: 16-04-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 14: Conflict of Interest Declaration for Clinician 14

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck (honoraria and research support combined)			X	
Janssen (Honoria and research support combined)			X	
GSK (honoraria)	X			

* Place an X in the appropriate dollar range cells for each company.