

October 23, 2023

Institute for Clinical and Economic Review  
One State Street, Suite 1050  
Boston, MA 02109 USA

**Public comments to ICER Draft Evidence Report for the Assessment of Sotatercept for Pulmonary Arterial Hypertension (PAH) released on September 25, 2023**

Dear ICER:

We would like to take the opportunity to provide comments on the ICER's draft evidence report for the assessment of sotatercept for PAH, released on September 25, 2023. Our comments are focused on both the clinical and economic aspects of the assessment, many of which have been previously communicated with ICER.

Herein, we will highlight the devastating nature of PAH and the potential transformative impact sotatercept may have on the lives of patients and their loved ones. Our comments will also describe the limitations of ICER's overall framework, which limits valuation for innovations targeting orphan diseases, specifically those which improve and extend the lives of those suffering from debilitating diseases like PAH. We will also reiterate recommendations we previously communicated to ICER regarding the use of inaccurate clinical assumptions and questionable economic model structure, which collectively have vastly underestimated the value sotatercept brings to patients, caregivers, the health care system and society.

Despite available treatments, the current PAH prognosis is poor, with rapid and unpredictable disease progression resulting in a median survival of only 5-7 years after diagnosis<sup>1-3</sup>. Current treatments for PAH do not address the underlying disease pathophysiology, representing a significant unmet need. PAH severely diminishes patients' survival, quality of life and daily functioning, and decreases independence<sup>4-7</sup>. Research has also revealed that the act of providing care for a PAH patient was frequently associated with exhaustion, an inability to work and subsequently a reduction of household income<sup>7</sup>.

Sotatercept, an activin signaling inhibitor, has the potential to help address the critical need in PAH, as it will be a first-in-class therapy that targets the underlying vascular remodeling<sup>8-10</sup>. Based on the robust clinical results from the Phase 3 STELLAR trial (40.8 meter improvement in 6MWD on top of current standard of care, 84% relative risk reduction for time to death or first occurrence of a clinical worsening event at a median follow-up of 32.7 weeks, 8/9 secondary endpoints met), sotatercept represents a true innovation in PAH<sup>10</sup>.

As detailed below, we recommend that ICER corrects its clinical assumptions, modify its model structure, and change the clinical evidence rating to an A.

## I. Clinical Assessment

### a. Clinical Benefits: Durability of Effect

ICER's reluctance to incorporate available data regarding durability of effect presents a critical gap in the overall assessment<sup>10-13</sup>. While we acknowledge uncertainty in clinical data and economic models, we believe ICER's failure to adequately incorporate available data into its assessment renders its clinical evidence review incomplete and biases its economic evaluation.

Merck has taken important steps to better understand the durability of effect of sotatercept. Some of these efforts are complete and others are ongoing; but collectively these data are beginning to provide evidence that addresses uncertainty about the long-term impact of sotatercept.

**Recommendation: While ICER acknowledges both long-term extension trials in its draft evidence report, it fails to appropriately contextualize the significance of the data emerging from these important studies.**

- 1. Replace the statement: “longer term data are needed to understand whether patients who continue sotatercept beyond 24 weeks continue to improve” with a more accurate representation of the available data from the long-term extension studies SOTERIA and PULSAR OLE, as well as STELLAR itself. Additional evidence suggests an estimated survival benefit of approximately 11.4 years with sotatercept on top of background therapy compared to background therapy alone<sup>5</sup>. Based on these data, ICER should reconsider its Net Health Benefit Rating.**
- 2. We urge ICER to reconsider its approach to more accurately reflect the totality of the available data to ensure it accurately characterizes the clinical evidence of sotatercept in the treatment of PAH.**
- 3. We ask that ICER revise its assessment and update its final report as additional data become available.**

### b. Clinical Benefits: 6-Minute Walk Distance (6MWD)

ICER based its primary analysis on median changes. Only later in the document does ICER refer to the more appropriate Hodges-Lehmann location shift results and even describes the Hodges-Lehmann approach as “more accurate.”

**Recommendation: ICER should use the 6MWD results based on the Hodges-Lehmann location shift given it was the primary, pre-specified registration analysis outlined in the STELLAR trial<sup>10</sup>.**

### c. Patient-Perspective: Quality of Life

The draft evidence report denotes on page 15 that “sotatercept did not appear to significantly impact overall quality of life as measured by the PAH-SYMPACT score, although both the Physical Impacts and Cardiopulmonary Symptoms scores were higher in the sotatercept group.”

The PAH-SYMPACT patient-reported outcome is a novel measure developed to better characterize patients' quality of life. Differences in both the physical impact and cardiopulmonary symptom scores are critical to

highlight as they represent substantial health burdens to PAH patients. Both the physical impact and cardiopulmonary symptom scores were significantly lower under treatment with sotatercept, indicating a patient-reported benefit from sotatercept. Both were part of the secondary endpoint hierarchy and are therefore associated with a p-value<sup>10</sup>. Without acknowledging the relevance of these two domains, ICER is diminishing the evidence of patient-reported improvement.

Please note that the physical and symptoms scores were not higher, as described by ICER in the draft evidence report, but lower in the sotatercept arm which shows lessening of physical impact and cardiopulmonary symptoms with sotatercept<sup>10</sup>.

**Recommendation:**

- 1. Add language to better contextualize findings from the PAH-SYMPACT patient-reported outcome measure. The disease-specific improvement observed with sotatercept should not be underestimated given it reflects a value dimension that is of critical importance to patients, their families and providers.**
- 2. Modify language to indicate “lower scores” instead of “higher scores” to correctly reflect the findings from STELLAR.**

**d. Results and Clinical Benefits: Improvement of Clinical Outcomes**

The draft evidence report (page 16) states, *“based on the currently available data, sotatercept added on to stable dual or triple background therapy appears to improve clinical outcomes for patients with PAH with a favorable side effect profile and less burdensome delivery system than many other current PAH treatments.”*

The language *“appears to improve clinical outcomes”* understates the magnitude of the relative risk reduction (84%) for time to death or first occurrence of a clinical worsening event, the 6MWD increase of 40.8 m, as well as meeting 8/9 secondary endpoints of the STELLAR trial<sup>10</sup>.

**Recommendation: Modify the language justifying the Evidence Rating to more accurately characterize the observed risk reduction in time to death or first occurrence of a clinical worsening event, include 6MWD findings and their collective significance to patients.**

**II. Economic modeling**

**a. Model Structure**

The current development of the economic model does not appropriately reflect various clinical aspects of PAH, including how patients and the intervention were studied in the STELLAR trial. ICER developed a decision analytic model for this evaluation, informed by old clinical trials and prior outdated economic models, relying primarily on models for vasodilator PAH drugs. Unlike current therapies, which are mainly vasodilators, sotatercept has the potential to be a disease-modifying agent. The STELLAR trial demonstrated that patients could move directly from intermediate-high risk to low risk (based on ESC/ERS guidelines), which ICER’s model structure does not allow.

## **b. Risk Strata Classification and Other Model Considerations**

ICER's economic model does not rely on the most recent risk strata classification approach for assessing PAH severity and progression. The risk strata classification is expected to provide more valid estimates compared to most prior models ICER references in its report and the current ICER model which relies on traditional WHO FC classification to predict long-term outcomes. More specifically, the WHO FC categories, ranging from FC I (most mild) to FC IV (most severe), have been and still are widely used by clinicians to classify PAH severity, predict survival, and measure treatment effectiveness. However, this clinician-rated classification approach presents certain limitations. In particular, it relies exclusively on clinicians' judgment of patient-reported symptoms, without accounting for objective measures of PAH severity. Additionally, WHO FC employs a single variable to measure disease severity, which may not fully capture patients' prognosis. As clinical assessment plays a vital role in the management of PAH, there is an immediate need for a more effective and objective assessment tool that can provide valuable insights into establishing the prognosis and severity of the disease. To address this, Merck shared post hoc analyses for risk strata from the STELLAR trial. However, ICER chose not to incorporate these data into this draft evidence report.

As we highlighted in previous interactions with ICER, the health economic evaluation is associated with inherent errors, in part due to the introduction of health states that do not reflect the STELLAR trial, such as differentiating between a and b in WHO FC III and IV (not established in clinical guidelines or current practice) or only being able to move to immediate neighboring states. Other errors include not including observed hospitalizations, reduction in PCA escalation and mortality benefit for sotatercept as shown in the STELLAR trial.

## **c. Survival Bias**

Despite the availability of published evidence, ICER's structure does not recognize that patients treated with sotatercept live longer. Furthermore, the implemented cost-effectiveness model penalizes increased survival as costs continue to incur in the sotatercept arm and therefore, results artificially appear less favorable for sotatercept.

## **d. ICER's Approach to Assessing Orphan Therapeutics**

Sotatercept is a transformative innovation that extends and improves the lives of patients with PAH. ICER's cost-effectiveness approach underestimates the true value provided by sotatercept given it fails to account for efficacy beyond 24 weeks which has been demonstrated in the long-term extension studies SOTERIA and PULSAR OLE, as well as in STELLAR itself<sup>10-13</sup>.

The willingness-to-pay-thresholds employed by ICER may be inappropriate for orphan diseases, obscuring the value of medicines such as sotatercept that improve the quality and quantity of life of patients with debilitating diseases like PAH. We recommend that ICER take a more dynamic approach to WTP thresholds similar to those proposed by the scientific community and applied by some assessment bodies. One possible way is to apply disease severity and disease rarity willingness-to-pay modifiers<sup>14-16</sup>.

### e. Therapeutic Pathways

It is important to recognize that after utilization of a PDE5i or an sGC stimulator and an ERA, distinct therapeutic pathways include the prostacyclin and the activin pathways. As for prostacyclin, effective synthetic prostanoids such as epoprostenol and treprostinil are used in SC or IV pumps or infusions, respectively. Selexipag is a prostacyclin receptor agonist. In general, prostacyclin agonists are more effective than prostacyclin receptor agonists in treating PAH. Given that selexipag is used as an oral agent, it is currently the preferred choice after PDE5i and ERA in most patients except the most severe. According to the 2019 CHEST PAH guidelines, selexipag was recommended for patients who have not responded to PDE5i and ERA<sup>16</sup>. Therefore, ICER's evaluation should include a range of therapeutic options, including those most relevant to aid in stakeholder decision-making. Considering the current standard of care, when selecting an appropriate therapeutic option following an initial dual combination regimen, the two viable choices should be between selexipag and sotatercept.

#### Recommendations:

- 1. Considering the relevant health policy question of whether to administer sotatercept instead of selexipag alongside PDE5i and ERA in newly diagnosed patients, we recommend conducting additional modeling that includes comparing the outcomes of sotatercept versus selexipag. This analysis could be conducted at least as a scenario analysis. In addition, we ask that ICER correct the price level of selexipag and other drugs. The table in the draft evidence report does not reflect the current list or net prices, partly with highly significant deviations.**
- 2. We recommend that ICER adopt disease severity and disease rarity-based willingness to pay thresholds that recognize the societal desire to help patients with devastating orphan diseases.**
- 3. We ask ICER to bring the impact PAH has on patients' and caregivers' lives to the independent appraisal committee upon any vote on the clinical or economic value of sotatercept.**

Thank you for the opportunity to comment on the Draft Evidence Report for the Assessment of Sotatercept for PAH. Based on the key points outlined above regarding additional evidence that demonstrate the value of sotatercept to the PAH patient community, we encourage ICER to revisit its approach to reflect both the existing data and ongoing efforts to understand the benefits of this novel intervention. If you have any questions, please feel free to reach out.

Sincerely,



Dr. Dominik Lautsch  
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October 23, 2023

Dr. Steven D. Pearson  
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Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment of treatments for Pulmonary Arterial Hypertension (PAH).

PAH is a rare, progressive disorder. Over time, a patient's heart loses the ability to effectively pump blood throughout the body. Even patients with well controlled PAH deal with serious impacts on their quality of life and are often forced to radically alter their lifestyles in order to manage their disease. There is currently no cure for PAH and there is a need for more effective treatments. As ICER conducts its assessment of treatments for PAH, PIPC urges it to consider the following comments.

### **ICER Continues to Use the Discriminatory QALY**

Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions<sup>1</sup> and people with disabilities.<sup>2</sup> There is widespread recognition that the use of the QALY is discriminatory. The QALY has historically been opposed by the American public and policy makers. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.<sup>3</sup>

### **ICER's chosen model does not lend itself to consideration of the PAH's heterogeneous patient population.**

ICER chose to use a health state transition model (HSTM), which is unable to evaluate heterogeneity of patients and the relative effectiveness of therapies on those populations. Given the heterogeneity of the PAH population, an individual patient simulation model would have been a better choice.

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<sup>1</sup> Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.

<sup>2</sup> Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.

<sup>3</sup> [https://www.ncd.gov/sites/default/files/NCD\\_Quality\\_Adjusted\\_Life\\_Report\\_508.pdf](https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf)

The model is also based on a single outcome, WHO-FC, which categories PAH into a small number of states. This over-categorization tends to hide marginal effects.<sup>4, 5</sup>

ICER had the ability to categorize health states by any number of outcome measures, and others may have been stronger choices. Specifically, ICER could have chosen to categorize by 6MWD, the primary endpoint in the STELLAR trial. The primary endpoint showed a 390% difference in effect for treated patients versus those on placebo whereas the relative improvement for WHO-FC showed just a 106% difference. It is concerning that ICER chose a secondary endpoint from the trial that had the smallest relative difference between treatment and placebo arms around which to build its model. This is also the outcome with the least sensitive measure of difference for patients with the disease, making an already simplistic model even more immune to relative difference.

**ICER excludes transplantation as an outcome of PAH, which leads to an underestimate of the value of effective treatment.**

ICER chooses to exclude transplantation as an outcome of PAH from the model. This is a major shortcoming as transplantations are burdensome on the patient and caregiver, of limited availability, and carry a significant cost. With all of this in mind, there is huge value – both economic and in terms of patient preference – to avoid a transplant. ICER’s choice to exclude the costs and outcomes associated with transplantation very likely led to underestimation of the true value of treating PAH patients with sotatercept.

**The durability assumptions in the model don’t adequately reflect the available evidence.**

The model makes an assumption that improvement can only occur over the first 24 weeks due to questions of uncertainty around the durability of the treatment beyond that shown in the STELLAR trial, yet subsequent and ongoing studies clearly shown durability to 18 and 24 months. Among patients continuing treatment in the PULSAR open-label extension trial, improvements in pulmonary vascular resistance, 6MWD, and NT-pro BNP were maintained over 18 to 24 months.<sup>6</sup>

**ICER assumes a linear relationship between severity of disease and utility increments, which is an approach that is losing validity among entities that practice value assessment.**

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<sup>4</sup> Naggara O, Raymond J, Guilbert F, Roy D, Weill A, Altman DG. Analysis by categorizing or dichotomizing continuous variables is inadvisable: an example from the natural history of unruptured aneurysms. *American Journal of Neuroradiology*. 2011 Mar 1;32(3):437-40.

<sup>5</sup> Bennette C, Vickers A. Against quantiles: categorization of continuous variables in epidemiologic research, and its discontents. *BMC medical research methodology*. 2012 Dec;12:1-5.

<sup>6</sup> Humbert M, McLaughlin V, Gibbs JSR, et al. Sotatercept for the treatment of pulmonary arterial hypertension: PULSAR open-label extension. *European Respiratory Journal*. 2023;61(1):2201347.



In recent years, there has been widespread reevaluation of several of the assumptions that cost utility analysis is built on.<sup>7</sup> This argument has been most prominent with respect to the reliance on the assumption that every unit of health gain – measured here in health-related quality of life - is equal in value.<sup>8</sup> In other words, a single unit of health generates the same utility whether that health is accrued to someone who is suffering considerable disease burden, or to someone who is suffering minimal disease burden.<sup>9</sup> In fact, several health technology assessment systems in Europe have backed away from direct use of strict cost-per-QALY estimates for this very reason, and incorporate the role of severity adjacent to the results to make a more context-relevant case for, or against, a new technology.<sup>10,11</sup>

PIPC would encourage ICER to follow this model and recognize that diseases that put a larger burden on patients and caregivers, like PAH, should be viewed differently than more common, less burdensome diseases.

## Conclusion

PIPC urges ICER to reconsider the use of the QALY along with several of its modeling choices given many of them do not accurately represent the pathway of a PAH patient or convey the potential value of an effective treatment.

Sincerely,



Tony Coelho  
Chairman  
Partnership to Improve Patient Care

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<sup>7</sup> Beresniak A, Medina-Lara A, Auray JP, De Wever A, Praet JC, Tarricone R, Torbica A, Dupont D, Lamure M, Duru G. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. *Pharmacoeconomics*. 2015 Jan 1;33(1):61-9.

<sup>8</sup> Sund B, Svensson M. Estimating a constant WTP for a QALY—a mission impossible? *The European Journal of Health Economics*. 2018 Jul;19(6):871-80.

<sup>9</sup> MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). *Social Science & Medicine*. 2018 Aug 1;211:359-66.

<sup>10</sup> Barra, M. and K. Rand-Hendriksen, *A missing cornerstone in the Norwegian Priority Commission's weighting scheme—Sub-treatment balancedness is a necessary property for priority setting criteria*. *Nordic Journal of Health Economics*, 2016. 4(2): p. pp. 8-23.

<sup>11</sup> Swedish Parliamentary Priorities Commission, *Priorities in health care: ethics, economy, implementation*. 1995, Stockholm: Swedish Government.



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October 23, 2023

**Comments on behalf of the Pulmonary Hypertension Association**

**RE: ICER Draft Evidence Report on Sotatercept for Pulmonary Arterial Hypertension**

The Pulmonary Hypertension Association (PHA) is the country's oldest and leading pulmonary hypertension (PH) organization. PHA's mission is to extend and improve the lives of those affected by PH. The organization achieves this by connecting and working together with the entire PH community of patients, families, health care professionals and researchers.

PHA's Scientific Leadership Council convenes expert PH physicians and researchers for scientific advancement and patient advocacy. PHA has a nationwide network of over 80+ accredited PH expert care centers treating adult and pediatric patients. The organization supports a national, observational patient registry, a network of 160+ patient support groups and a wide variety of additional support, education and advocacy opportunities for those living with PH and their loved ones. PHA routinely coordinates with other global leaders in the PH, rare disease and respiratory disease spaces.

PHA appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report related to sotatercept for treatment of pulmonary arterial hypertension (PAH).

**PAH Patient Experience and Burden of Disease**

PHA appreciates the time and attention ICER staff dedicated to better understanding the life-changing experience of a PAH diagnosis and the tremendous, ongoing burden of this chronic, progressive, life-threatening condition.

As the Draft Evidence Report notes, PAH is a progressive disease that can dramatically reduce quality of life and substantially shorten life span. Delays in diagnosis are common because of non-specific initial symptoms and poor awareness about the disease among clinicians and the general public. PAH patients often spend years seeking an accurate diagnosis, visiting multiple specialists and experiencing a progressive decline in their ability to work, engage in community activities and care for themselves. Due to the progressive nature of PAH, any delay or disruption in treatment risks reduced functionality that may not be recovered even with appropriate treatment.

More than 70% of individuals with PAH are in an advanced stage of the disease (functional class III or IV on a scale of IV) by the time they are accurately diagnosed and must start on complex, burdensome treatment regimens<sup>1</sup>. While several PAH therapies are available in pill form, other therapy options require complex administration, for example, regular preparation by the patient in a sterile environment; extended administration multiple times a day and/or continuous infusion. Common side effects of PAH therapies include but are not limited to GI concerns (nausea, vomiting, diarrhea), injection site pain, jaw pain, leg pain, headaches, lightheadedness and dizziness, flushing and rash. Medication administration complexity and side effects can be debilitating and keep people with PAH homebound even when their disease-specific symptoms have improved.

In addition, many people with advanced PAH benefit from supplemental oxygen, however insurance limitations and other barriers result in individuals receiving less oxygen than they need for daily activities as well as sub-ideal oxygen delivery equipment. People living with PAH, who are already short of breath and fatigued, are expected to move heavy, bulky oxygen tanks, creating a situation where time away from home, when it is possible at all, is severely restricted and physically and emotionally demanding.

Due to a combination of disease symptoms and treatment burden, many PAH patients are forced to leave work they value and apply for disability benefits.

These dramatic changes in physical health and social connection make mental health concerns such as depression and anxiety common experiences for those living with PAH – experiences that their PH-focused clinicians may not think to, or be equipped to, help resolve. Insurance challenges and other barriers to treatment exacerbate the mental health burden of PH as patients worry that they may not receive their life-sustaining medication.

The burden of PAH extends not just to individuals living with the condition, but also to their family members, loved ones and communities who are impacted by the physical, financial and emotional costs of the disease.

### **New Pathway and Potential for Disease Modification**

As mentioned in the Draft Evidence Report, sotatercept is a first-in-class therapy, addressing a unique pathway in the treatment of PAH. Sotatercept presents the possibility of clinical improvement after 24 weeks and the potential to be disease modifying.

**PHA encourages ICER to consider data beyond 24 weeks in the PULSAR open-label extension and interim results from the SOTARIA open-label extension, which strongly suggest sustained benefit beyond 24 weeks<sup>2,3</sup>.**

Data from these studies shows striking, multi-component improvement, even among patients who were considered stable on background therapy, and suggests reduced need for parenteral therapy, a change that could simultaneously improve PAH patients' quality of life and decrease health care system costs.

In addition, the drug was very well tolerated, with 92% of PULSAR participants continuing into the open label extension.

PHA believes that limiting access to sotatercept at this time would limit the opportunity to observe for:

- disease modification, particularly when sotatercept is started early in disease progression
- reduced health care costs, both to the individual and society

### **A New Option for Vulnerable, Under-Treated Patients**

While clinical trials for sotatercept focused on adding it to standard of care, ICER should also consider its potential for patients who are currently under-treated due to adherence barriers.

Treatment for advanced PH includes therapies with complex administration mechanisms and significant side effects. Currently, expert PAH clinicians encounter patients who are unable to sustain adherence on these therapies due to housing instability, physical or cognitive limitations, lack of caregiver support or other reasons.

Sotatercept's delivery mechanism, an injection every three weeks, is currently unique among PAH therapies and has the potential to increase both adherence and quality of life for patients who struggle with adherence to existing advanced therapy options.

### **Prioritizing PAH Care Driven by Clinical Judgement**

PAH is a complex disease with multiple pathological mechanisms and its management is even more complex. PAH therapies fall into several classes of drugs, operating on different disease mechanisms. **Even within classes, patients may respond differently to different therapy options.**

As described above, PAH therapies in general are also associated with significant side effect burden and the mechanism of administration varies, impacting how well different patients can adhere to treatment regimens.

Due to the progressive nature of PAH, finding and initiating appropriate therapy is urgent. Any treatment delay includes the potential for the patient to lose functionality that they are not able to fully recover, even once appropriate treatment is initiated.

For these reasons, PHA prioritizes care driven by expert clinical judgement and the patient-clinician relationship. All PAH patients should have prompt access to the FDA-approved therapies prescribed by their expert clinician. Barriers that exacerbate treatment delay by interfering with immediate access to the prescribed therapies should be reduced, and whenever possible, eliminated.

Ultimately, PHA encourages all stakeholders to invest in robust access to sotatercept, with uptake driven by expert clinical judgement and the patient clinician relationship.

## References

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