Subject: Response to 12-Month Follow-up for Evidence Regarding "Sotatercept for Pulmonary Arterial Hypertension – Final Evidence Report"

Dear ICER,

We appreciate the opportunity to submit new evidence regarding Sotatercept (WINREVAIR), since the report 'Sotatercept for Pulmonary Arterial Hypertension" was published on January 8, 2024.

Clinical Evidence:
We outline the key findings from recent clinical trials. These reinforce the significant and sustained positive patient impact of sotatercept. We further conducted post-hoc analyses on RCT data (i.e. STELLAR) that demonstrate the consistency of efficacy of Sotatercept across subgroups of PAH patients.

New Clinical Trial Findings:

1. **ZENITH:** In a phase 3 RCT of high-risk adults with pulmonary arterial hypertension who were receiving the maximum tolerated dose of background therapy, treatment with sotatercept resulted in a 76% lower risk of a composite of death from any cause, lung transplantation, or hospitalization ($\geq$ 24 hours) for worsening pulmonary arterial hypertension than placebo (trial stopped early on basis of efficacy of a prespecified interim analysis). [1]
2. **HYPERION:** Phase 3 HYPERION trial evaluating WINREVAIR™ (sotatercept-csrk) was stopped early, moving to final analysis due to "loss of clinical equipoise" [2]. The data is to be presented later in 2025.
3. **STELLAR + SOTERIA**: A recent analysis from STELLAR and SOTERIA trials, using Cox proportional hazards to model survival, showed 83% reduction (p=0.037) in risk of mortality for patients on sotatercept compared to placebo [3].
4. **SOTERIA**: Improvements in 6MWD, NT-proBNP, WHO FC, and SFRS achieved from baseline of SOTERIA were largely maintained at both one and two years follow-up, including in the placebo-crossed group.[4,5]
5. **PULSAR + SPECTRA + STELLAR + SOTERIA**: In conjunction with preliminary data demonstrating durability of efficacy, these exposure-adjusted safety data from a pooled dataset of sotatercept clinical trials support that the positive benefit-risk profile of sotatercept is maintained with longer-term treatment. [5]

Post-Hoc Analyses of STELLAR:

1. In an evaluation of responder thresholds for PAH-SYMPACT, more participants in the sotatercept versus placebo group met or exceeded the responder thresholds at week 24, with the between-group differences in proportions reaching statistical significance for the cardiopulmonary and cardiovascular symptoms domain scores [6].

2. In a post-hoc analysis to understand the prognostic value of the multicomponent improvement (MCI) endpoint, participants treated with sotatercept vs. placebo were significantly less likely to experience a fatal or nonfatal clinical worsening event, even when they did not meet the MCI endpoint [7].
3. Post-hoc analyses conducted on subgroups of STELLAR patients - by cardiac index group [8], presence of cardiometabolic comorbidities [9], background therapy [10] and risk strata [11] - all demonstrated consistency of efficacy of sotatercept across subgroups. Safety profiles were generally consistent across subgroups.

New Real-World Evidence to Support the Broader Value of Innovation in PAH

Real-world evidence studying the burden of PAH in subgroups of PAH patients who experience significant disease burden – those with comorbidities [12, 20], women of childbearing age [13-16], caregivers of PAH patients [17-18] and those facing greater financial burden [19, 21-22] - further demonstrate the potential value of a disease-modifying innovation such as Sotatercept.

Thank you for the opportunity to provide updated evidence regarding the value of sotatercept.

Sincerely,

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Response to Post-Assessment Follow Up:
ICER Report on Sotatercept for Pulmonary Arterial Hypertension

Submitted by: Pulmonary Hypertension Association

May 28, 2025

In ICER's December 2023 report, *Sotatercept for Pulmonary Arterial Hypertension*, ICER described their final assessment of sotatercept in this way:

"Based on the currently available data, treatment with sotatercept added to background therapy can improve clinical outcomes for patients with PAH, with relatively few harms. … However, uncertainty remains about sotatercept's efficacy in sicker populations and in those with connective tissue disease, and about the durability of effect. In the absence of longer-term data, we necessarily have uncertainties about sotatercept's effects on mortality and as-yet-undetected adverse effects."

Since then, data from these two studies have provided additional information about the drug's safety and efficacy in sicker populations and its durability of effect.

ZENITH

ZENITH, a pivotal, phase 3 trial of sotatercept, enrolled 172 PAH patients in the advanced state of the disease (functional class 3 and 4), with high risk of mortality.

According to results from the ZENITH study, presented during a Clinical and Investigative Horizons session at ACC.25 in Chicago and simultaneously published in the New England Journal of Medicine[1], Sotatercept added to background therapy in functional class 3 and 4 PAH patients led to a **76% lower risk** of:

- a composite of death from any cause
- lung transplantation
- hospitalization for worsening pulmonary arterial hypertension

These results are when compared to placebo in adults with PAH at high risk of mortality.

SOTERIA

SOTERIA is an ongoing open-label extension study evaluating the long-term safety, tolerability and efficacy of sotatercept when added to background therapy for the treatment of PAH in patients who have completed previous sotatercept studies without early discontinuation.

Improvements in 6-minute walk distance, NT-proBNP, World Health Organization functional class and Simplified French Risk Score Model achieved from baseline of SOTERIA were largely maintained at one year, including in the placebo-crossed group.

Of 426 participants, 387 (90.8%) experienced AEs, 15 (3.5%) discontinued treatment, 129 (30.3%) had serious AEs, and 11 (2.6%) had serious AEs related to treatment. There were 12

deaths (2.8%). Among AEs of interest, epistaxis (22.1%) and telangiectasia (16.9%) were the most frequently reported individual events. Twenty-two (5.2%) participants had serious bleeding events.

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