Sotatercept for Pulmonary Arterial Hypertension: Response to Public Comments on Draft Evidence Report

November 14, 2023

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#	Comment	ICER Response
Manufacturers		
Merck & Co.		
1.	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[1-3]. 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[4-7]. 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[7]. 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[8-10]. 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[10]. As detailed below, we recommend that ICER corrects its clinical assumptions, modify its model structure, and change the clinical evidence rating to an A.	Thank you for this comment. We appreciate the comments emphasizing the severity of PAH and its impact on patients, which we have tried to convey in our report. While we agree that the STELLAR trial provides evidence that sotatercept can improve clinical outcomes for patients with WHO FC II and III on background therapy, there is remaining uncertainty about the durability of its effects. We appreciate the additional long-term data from the SOTERIA open-label trial provided to us by the manufacturer and have added these data to the report; however, these are non-peer reviewed interim results, with uncertainty around the results due to large standard deviations around estimates. Furthermore, few clinical worsening events occurred, and sotatercept's impact on mortality is still uncertain. Studies have shown that the addition of black box warnings in postmarketing surveillance is not uncommon.[1,2] ICER's Evidence Rating and model structure both acknowledge sotatercept's impact on improving clinical outcomes for individuals with PAH and appropriately capture the uncertainty around the impact of sotatercept on mortality and its long-term harms. ICER views a B+ rating as a very favorable rating for a new therapy.
2.	Clinical Benefits: Durability of Effect ICER's reluctance to incorporate available data regarding durability of effect presents a critical gap in the overall assessment[10-13]. While we acknowledge uncertainty in clinical data and economic models, we believe ICER's failure to adequately incorporate available data into its	We have revised our report to reflect the newer long-term follow-up data from the SOTERIA trial. However, as mentioned above, there is still uncertainty around sotatercept's long-term outcomes. The data presented from the interim SOTERIA analysis showed large standard deviations around the estimates for change in 6MWD and NT-

	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. <u>*Recommendation*</u>: 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[5]. 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.	proBNP; additionally, a percentage of patients on sotatercept either required an increase in or addition of another PAH medication, leaving uncertainty about how durable sotatercept's effects are. Some of the clinical experts we spoke with during the review also expressed reservations about whether sotatercept should be considered a disease-modifying agent without more long-term data. Thus, we await additional peer-reviewed data both from the SOTERIA interim analysis and from further follow-up of SOTERIA patients. The manufacturer found no statistically significant improvement in mortality in their 24-week randomized trial data. They then modeled a mortality reduction leading to an additional 11.4 years of life. We do not feel it is appropriate to credit a new therapy with this degree of life extension given the existing data. ICER instead modeled reductions in mortality based on change in functional class, and even this life extension is assuming an unproven benefit. ICER has a routine process that allows information on new data to be included at 12 months. Should data demonstrating 11.4 year life extension become available at any point in the future, this would, of course be important to include.
3.	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." <u>*Recommendation*</u>: 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[10].	We have revised the Executive Summary to reflect the Hodges-Lehmann estimate for the 6MWD results.

4.	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[10]. 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[10]. <u>*Recommendation*</u>: 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. Modify language to indicate "lower scores" instead of "higher scores" to correctly reflect the findings from STELLAR	We have corrected the higher/lower description of the physical impact and cardiopulmonary PAH-SYMPACT domains. Thank you for the correction. While we recognize the importance of patient-reported outcomes (PRO) and commend the manufacturer for its use of a disease-specific PRO in the STELLAR trial, the minimal clinically important difference for the PAH-SYMPACT has not been established. Additionally, there was a high proportion of missing values (over 40%) for this measure. Thus, there remains some uncertainty about both the clinical relevance and statistical validity of the observed results from the PAH-SYMPACT measure.
5.	Results and Clinical Benefits: Improvement of Clinical Outcomes The draft evidence report (page 16) states, "*based on the currently available data, sotatercept added*	As noted above, we have revised our report to better reflect sotatercept's impact on clinical outcomes.

	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[10]. *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.	We have reported the 84% relative risk reduction for the composite endpoint of time to death or first occurrence of a clinical worsening event in the report. However, we also note that composite endpoints can be misleading, particularly when the combined endpoints are heterogeneous, occur at different frequencies, or the treatment effects differ for each of the components. Thus, we remain cautious in interpreting the composite endpoint in the STELLAR trial.
6.	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.	In conversations with clinical experts, we heard that transitions to non-adjacent functional classes within a 12-week period (i.e., one model cycle) are very unlikely and those that have been reported in the literature were likely right on the cutoff line and are more reflective of a one-step change rather than a two-step change when considering outcomes. Further, using the academic in confidence data provided by Merck, the number of patients that went from FC III to FC I was very small and occurred in both arms of the trial so it would not have a large impact on the model. We have also conducted and reported numerous optimistic scenario analyses that assumed different structural assumptions around the potential for sotatercept to be disease modifying. However, numerous clinical experts expressed reservations on the disease modifying nature of sotatercept, which is why the duration of functional class improvement was limited to the duration of available evidence in the base-case.
7.	Risk Strata Classification and Other Model Considerations	The population health model published by Merck co-authors had health states defined by the risk strata classification approach. Even though our

	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.	model had health states defined by the commonly used WHO functional class classifications, the model outcomes between the Merck model and the ICER model approximated each other when other model assumptions and inputs (besides whether health states were defined by functional class or risk strata) were modeled as the same. This would suggest that having health states defined by risk strata or WHO functional class does not dramatically influence the findings. We appreciate Merck sharing the post hoc analyses for risk strata and for WHO functional class from the STELLAR trial. We used the direct data Merck provided for WHO functional class in the model and compared our findings to Merck's model that used the risk strata data as a structural sensitivity test and validity check. Differentiating between a and b in WHO FC III and IV was for the purposes of transparency and cohort tracking for the model purposes only. It was a clear and transparent way to build history into the model to allow for people to improve in functional class after starting an infused prostacyclin.
8.	Survival Bias	As stated in the report, ICER's model does not assume an independent effect of sotatercept on

	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.	mortality due to the small sample size, short timeframe, double counting with mortality benefits downstream of functional class improvement, and most notably, the hazard ratio on all-cause mortality for sotatercept was not statistically significant. We also present findings that exclude all non-treatment-related costs which is a non-realistic assumption that greatly benefits sotatercept.
9.	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[10-13]. 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[14-16].	We have also conducted and reported numerous optimistic scenario analyses that assumed different structural assumptions around the potential for sotatercept to be disease modifying. However, numerous clinical experts expressed reservations on the disease modifying nature of sotatercept, which is why the duration of functional class improvement was limited to the duration of available evidence in the base-case. ICER provides cost-per-evLYG and per QALY results at $50,000, $100,000, $150,000 and $200,000 for all assessments, including those for treatments of ultra-rare disorders. The size of the population for pulmonary arterial hypertension did not fall under ICER's ultra-rare adaptations. As part of ICER's newly released Value Assessment Framework, ICER will undertake a special focus in the coming months on considering novel ways to quantify preferences related to severity, methods that often are framed as abandoning an assumption of a linear relationship between health gain value and replacing it with a formula that can capture risk aversion, severity, and the value of insurance. ICER will be focusing on generalized risk-adjusted cost-effectiveness and methods adopted by other international HA programs that weight health gains in relation to severity.
10.	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	We agree that clinical guidelines present a range of choices on the addition of a 3rd agent for individuals who require therapy beyond a PDE-5i or sGC stimulator and an ERA. However, during our

	the activin pathways. As for prostacyclin, effective synthetic prostanoids such 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[16]. 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.	interviews with clinical experts, they conveyed that there is substantial variation in the choice of 3rd agent, depending partly on the clinical situation and patient preferences, and that while selexipag was sometimes used, it is not necessarily the used as the 3rd agent in all situations. Additionally, we have not found data directly comparing adding sotatercept as a 3rd agent vs selexipag. Until data comparing selexipag and sotatercept become available, we felt it was not appropriate to have selexipag as a separate comparator in this review.
11.	*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.	The comparator in economic models is based on current standard of care, and we did not hear from clinical experts that selexipag represents current standard of care. This model will be going into ICER's Interactive Modeler where inputs to the comparator can easily be modified by users. The drug prices we report in Table E13 are based off the wholesale acquisition cost (WAC) in RED BOOK and have a WAC to net price discount based on SSR Health. This aligns with ICER's reference case. From your comment, it is not clear which drugs you are suggesting are incorrect, which drug cost you are suggesting as an alternate, or what source you are using. If you could provide us that information, we would certainly take it under advisement.
12.	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.	As part of ICER's newly released Value Assessment Framework, ICER will undertake a special focus in the coming months on considering novel ways to quantify preferences related to severity, methods that often are framed as abandoning an assumption of a linear relationship between health gain value and replacing it with a formula that can

		capture risk aversion, severity, and the value of insurance. ICER will be focusing on generalized risk-adjusted cost-effectiveness and methods adopted by other international HA programs that weight health gains in relation to severity.
13.	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.	As the manufacturer is well aware, ICER will bring these issues and others to votes of the independent Midwest CEPAC. These votes will include a vote on the economic value of sotatercept if the manufacturer provides a price or price range to ICER prior to the meeting. Additionally, we believe it would be unfortunate if the manufacturer continues with plans not to participate in the policy discussion at the meeting of the Midwest CEPAC as transparency requires all parties to participate and open themselves to questions and debate.

#	Comment	ICER Response
Patients/Patient Groups		
Pulmonary Hypertension Association (PHA)		
1.	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 SOTERIA open-label extension, which strongly suggest sustained benefit beyond 24 weeks[2,3]. 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	We appreciate this feedback. As mentioned above, we have now revised the report to reflect the results from the PULSAR and SOTERIA open-label extension trials. With regard to the disease-modifying potential of sotatercept, clinical experts we spoke with during the review expressed cautious optimism about sotatercept but felt that additional data was warranted before making conclusions. We conducted and reported numerous optimistic scenario analyses that assumed different structural assumptions around the potential for sotatercept to be disease modifying. One of these allowed for treatment improvement over a lifetime. Another assumed whatever functional class an individual was in at 24 weeks, they would remain there over their lifetime. However, numerous clinical experts expressed reservations on the disease modifying nature of sotatercept, which is why the duration of functional class

	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	improvement was limited to the duration of available evidence in the base-case.
2.	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.	We appreciate that PHA continues to highlight the health disparities that exist for some individuals with PAH. We have discussed how sotatercept's mechanism of action has the potential to decrease health disparities in Section 5 of the report (Contextual Considerations and Potential Other Benefits). We have also highlighted how a simpler regimen may benefit patients and allow them more flexibility in their lives in Section 2 (Patient and Caregiver Perspectives).
3.	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. <u>Even within classes, patients may respond differently to different therapy options.</u>	We agree with this comment and appreciate that PHA continues to advocate for fair access to effective treatments.

	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.	

#	Comment	ICER Response
Other		
Partnership to Improve Patient Care		
1.	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 and people with disabilities. 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.	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues your raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value.
2.	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. 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. 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	The model structure was based on WHO functional class which is a clinician-rated assessment used widely to assess PAH severity and functioning. Extensive research, spanning decades, has been conducted on determining costs and consequences based on WHO functional class.

	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.	
3.	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 trial for sotatercept suggested no difference between sotatercept and background therapy in listing for lung or heart transplantation.
4.	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.	We conducted and reported numerous optimistic scenario analyses that assumed different structural assumptions around the potential for sotatercept to be disease modifying. One of these allowed for treatment improvement over a lifetime. Another assumed whatever functional class an individual was in at 24 weeks, they would remain there over their lifetime. However, numerous clinical experts expressed reservations on the disease modifying nature of sotatercept, which is why the duration of functional class improvement was limited to the duration of available evidence in the base-case.
5.	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. In recent years, there has been widespread reevaluation of several of the assumptions that cost utility analysis is built on. This argument has been most prominent with respect to the reliance on the	As part of ICER's newly released Value Assessment Framework, ICER will undertake a special focus in the coming months on considering novel ways to quantify preferences related to severity, methods that often are framed as abandoning an assumption of a linear relationship between health gain value and replacing it with a formula that can capture risk

	assumption that every unit of health gain – measured here in health-related quality of life - is equal in value. 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. 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. 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.	aversion, severity, and the value of insurance. ICER will be focusing on generalized risk-adjusted cost-effectiveness and methods adopted by other international HA programs that weight health gains in relation to severity.

1. Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *Jama.* 2017;317(18):1854-1863.
2. Solotke MT, Dhruva SS, Downing NS, Shah ND, Ross JS. New and incremental FDA black box warnings from 2008 to 2015. *Expert Opin Drug Saf.* 2018;17(2):117-123.