To whom it may concern,

I am a nurse practitioner with a doctorate degree and have been working exclusively with pulmonary hypertension (PH) patients for the past 23 years.

I am writing to provider expert comments around sotatercept , the newest drug likely to enter the PH market soon. In my 23 years of experience this is the most promising drug to potentially enter the market since the first oral medication was FDA approved in 2002. What is especially advantageous about this new treatment is that it is a new mechanism of action and one that may prove to be disease modifying where current FDA approved therapies are all vasodilators which don't mitigate the actual disease process. Currently pulmonary arterial hypertension remains a progressive fatal disease.

Sotatercept would likely be an add on therapy after PDE5i and ERAs. Current practice is to advance care with a prostacyclin therapy which carries complex administration challenges as well as a significant side effect burden. Sotatercept is an injection given every 21 days with minimal side effects thus far seen in clinical trials, especially compared with prostacyclin pathway therapies. This has the potential to be less burdensome for caregivers than prostacyclins which are often administered using infusion pumps through central line catheters. Intravenous prostacyclins carry risk for central line infections which are not rare and result in costly hospitalizations. Sotatercept will not have that societal burden.

In the STELLAR trial not only was the primary endpoint met but also 8 of 9 secondary endpoints were met, something we have not seen before in PH clinical trials. The study showed effectiveness with regard to walk distance, improvement in NT pro BNP, functional class, pulmonary vascular resistance, time to clinical worsening and risk scores.

I believe this new therapy in a new treatment pathway gives patients and providers a great deal of hope for the course of the disease. I suspect most patients will benefit from this therapy regardless if they are receiving monotherapy, dual or triple therapy.

Martha Kingman, FNP, DNP
Dallas TX.

June 2nd, 2023

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

Public comments to ICER Draft Scoping Document for the Assessment of Sotatercept for Pulmonary Arterial Hypertension (PAH) released on May 15, 2023

Dear Dr. Pearson:

Thank you for the opportunity to provide comments on the draft scoping document for the assessment of Sotatercept for PAH released on May 15, 2023. We would like to focus on 3 areas: Population, comparator, and scope of the comparative value analysis.
Please find below our recommendations and associated rationale.

1. Population and comparator

1.1. Population

The draft scoping document defines the target population as "*patients… on stable background therapy, defined as monotherapy or combination therapy of agents from the following classes: endothelin receptor antagonists (ERA), phosphodiesterase 5 Inhibitors (PDE5i), soluble guanylate cyclase stimulators (sGC), prostacyclin analogues (prostanoids)*".

***Recommendation*: Given current guidelines, results of STELLAR and expertise by the clinical leaders in the field we recommend utilization of sotatercept as an early addition to a generic regimen, such as PDE5i and/or ERA. This best reflects current healthcare policy and expected future clinical standards**.

While the results of STELLAR indicate a consistent clinical benefit of sotatercept across all subgroups of background therapies, future clinical practice is expected to use sotatercept directly after a generic regimen which includes a PDE5i and/or an ERA.[4]

For patients with low or intermediate risk and no cardiopulmonary comorbidities, the current clinical guidelines, the 2022 European Society of Cardiology (ESC) / European Respiratory Society (ERS) guidelines on Pulmonary Hypertension (see section 5.2 for the treatment

algorithm),[1] recommend initial ERA+PDE5i dual combination therapy.[1] This recommendation is consistent with the recommendations from the 6th World Symposium on Pulmonary Hypertension and the 2019 American College of Chest Physicians (CHEST) guidelines.[2,3]

According to ESC/ERS guidelines (Figure 9, p. 3666), in patients already on an ERA/PDE5i combination regimen, addition of selexipag has the highest evidence (level IIa) and recommendation rating as a next step.[1-3] The addition of selexipag in this manner has also been confirmed by discussions with clinical experts in the field.[5]

In the recent ERS/ESC 2022 guidelines, parenteral or inhaled prostacyclin therapy is reserved for the most advanced patients – those at high risk or intermediate-high risk after failure of prior therapies.[1] This placement is consistent with the earlier 6th WSPH, which positions these therapies after selexipag in the case of a lack of effectiveness.[2]

1.2. Comparator

The draft scoping document defines the targeted comparators and mentioned selexipag as a potential comparator, stating, "*If the clinical review suggests that sotatercept may displace other additive therapies (e.g., selexipag) in the usual course of clinical care, that may be modeled.*" The document also states "*Unlike current therapies, which are mainly vasodilators, sotatercept has the potential to be a disease-modifying agent*", indicating its value for earlier use after initial generic regimen.

Recommendation: Using sotatercept instead of selexipag on top of PDE5i and ERA in newly diagnosed patients is the relevant health policy question. **We recommend modeling sotatercept versus selexipag as the primary analysis**.

.

After utilization of a PDE5i and/or an ERA, drugs acting on the prostacyclin pathway are available as add on treatments. Available therapies targeting that pathway include synthetic prostanoids such as epoprostenol and treprostinil, which are used in SC or IV pumps or infusions, respectively, but are associated with a burden of adverse events.[1] Selexipag has a different mode of action as it is a prostacyclin receptor agonist and therefore not a prostanoid. As indicated above, selexipag is used as an oral agent and is currently the preferred choice immediately after PDE5i and ERA in most patients except the most severe ones. [1-3]

2. Scope of Comparative Value Analyses

PAH is an aggressive, rare, and progressive disease that affects patients, families, and society. Therefore, with respect to comparative value analyses, we would like to highlight the nature of the

disease that might warrant an adapted assessment including a willingness to pay threshold of above USD 200.000 because of both (a) the rarity of PAH and (b) the severity of PAH. Such adaptations allowing for a more dynamic approach to WTP thresholds have been proposed by key health economists and are applied by some HTA bodies.[6-9]

2.1 Time Horizon

The draft scoping document specifies the preference in assessing "*the lifetime cost-effectiveness of sotatercept*."

Recommendation We recommend **ICER use a 10-year horizon as the base case** and a lifetime horizon as a scenario analysis.

Given the median survival of 5-7 years after a diagnosis with PAH, as ICER acknowledged in the scoping document, the expected lifetime horizon for patients living with PAH is significantly less than in patients living with many other diseases. It is currently estimated that only 30% of patients survive beyond year 9.[10] Thus, limiting the time horizon of the model to 10 years will best reflect current survival trends in PAH.
Therefore, even if the base case remains lifetime, we recommend to model over ten years at least as a scenario analysis.

Thank you again for this opportunity to provide comments and we look forward to continuing this engagement throughout the assessment period. If you have any questions, please feel free to reach out.

Sincerely,

Dr. Dominik Lautsch
Senior Director,
Center for Observational and Real-World Evidence
Merck & Co., Inc., Rahway, NJ, USA
Email: dominik_lautsch@merck.com; Tel: +1 (267) 742-1987

3. References

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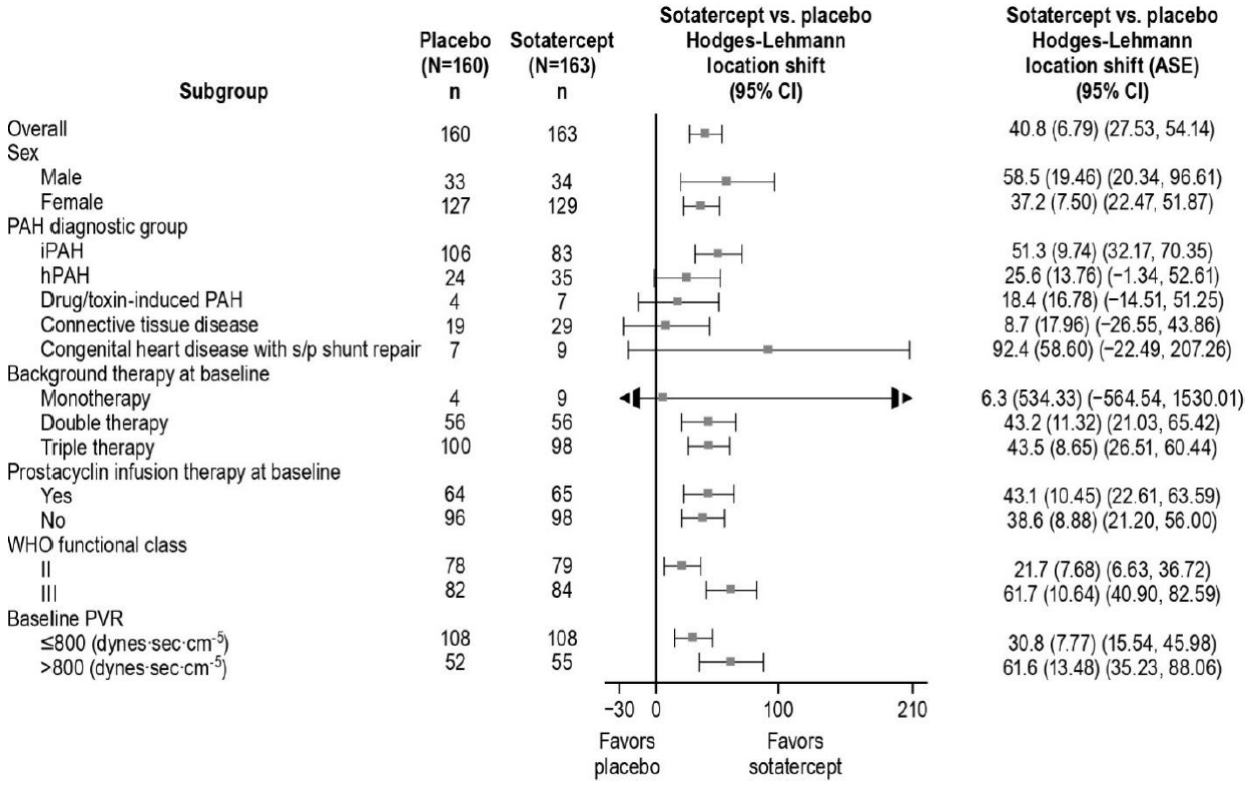
4. Supplementary materials

4.1. Clinical benefits of sotatercept across the background of mono-, dual-, and triple-therapy

As shown in STELLAR, the relative treatment effect (between sotatercept + background therapy versus placebo + background therapy) is consistent across utilization on the background of dual and triple therapy in terms of 6-minute walk distance (6MWD; Figure 2), N-terminal pro–B-type natriuretic peptide (NT-proBNP; Figure 3), World Health Organization (WHO) functional class (FC) improvement , and WHO FC worsening .

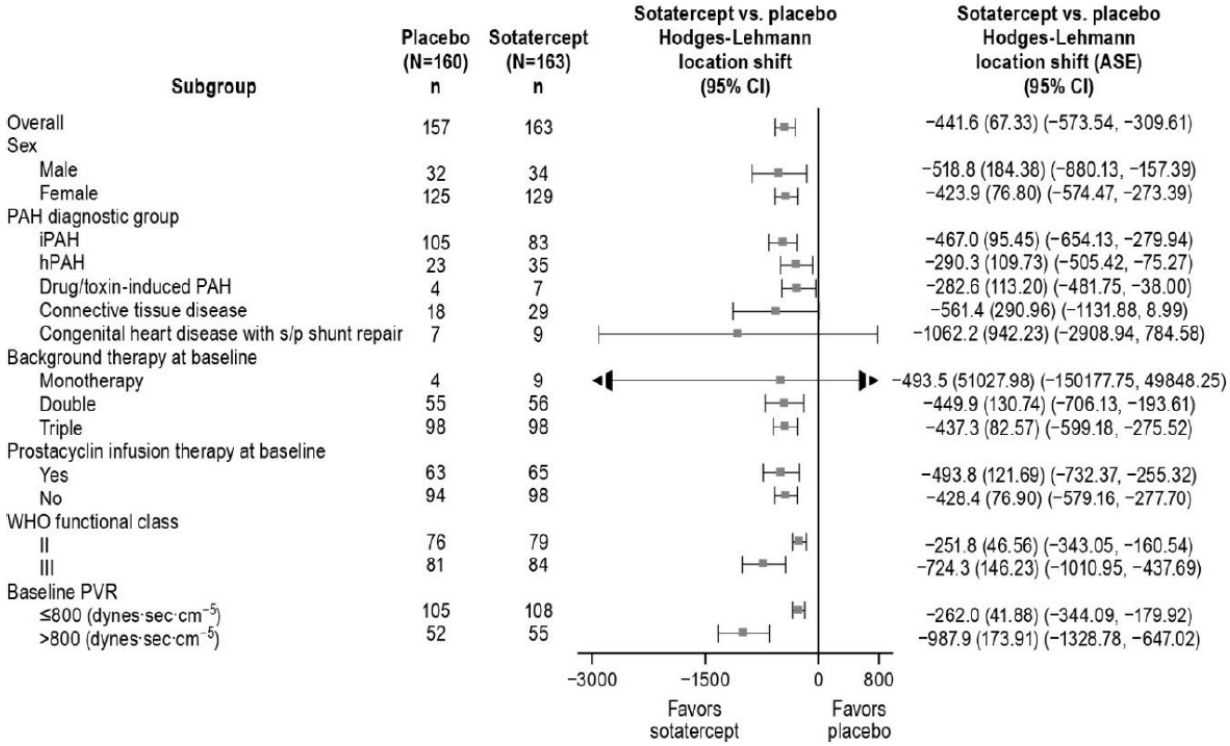
Figure 1. Relative Treatment Effect of Sotatercept + Background Therapy vs Placebo + Background Therapy on Change from Baseline at Week 24 in 6MWD Results by Prespecified Subgroup



Source: STELLAR[4]

6MWD, 6-minute walking distance; ASE, asymptotic standard error; CI, confidence interval; hPAH, heritable pulmonary arterial hypertension diagnosis; iPAH, idiopathic pulmonary arterial hypertension diagnosis; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SoC, standard of care; WHO, World Health Organization

Figure 2. Relative Treatment Effect of Sotatercept + Background Therapy vs Placebo + Background Therapy on Change From Baseline at Week 24 in NT-proBNP by Prespecified Subgroup

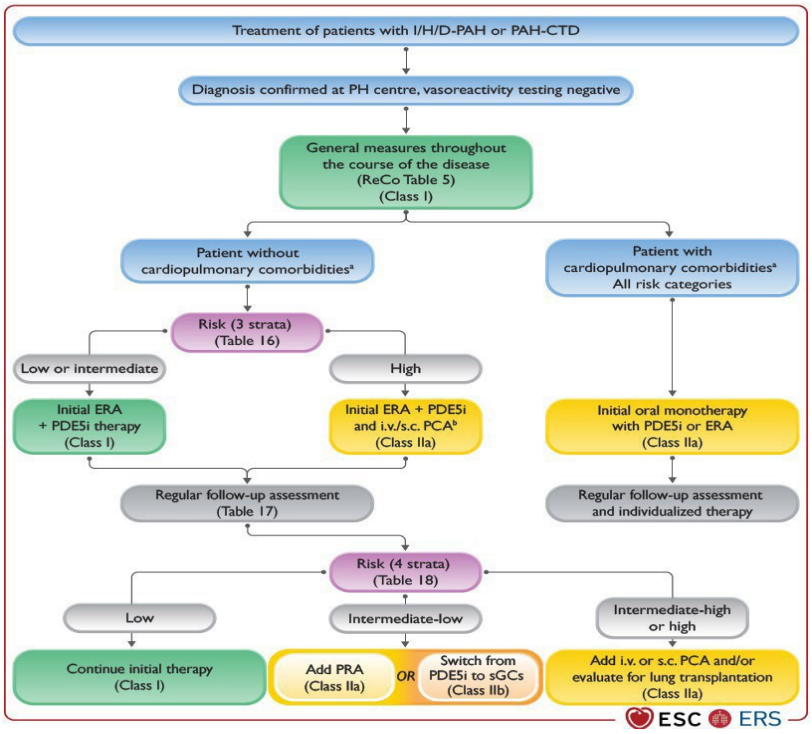


Source: STELLAR[4]

ASE, asymptotic standard error; CI, confidence interval; hPAH, heritable pulmonary arterial hypertension diagnosis; iPAH, idiopathic pulmonary arterial hypertension diagnosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SoC, standard of care; WHO, World Health Organization

4.2. Treatment algorithm

Figure 3. Current Treatment algorithm, ESC/ERS 2022 guidelines



Reference: 2022 European Society of Cardiology (ESC) / European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension[1]

Dr. Marc Simon

One minor comment: if you are going to mention the French risk score as an outcome of interest then you should really also mention the REVEAL risk score.

Hi Yamaya,

I attach some suggested edits in your scoping document in terms of the messaging around sotatercept. In particular, I am opposed to going down the pathway of 'disease modifying' – while I understand that Merck and many of my colleagues are keen on this, I think that the presently available drugs do more than vasodilate and just because sotatercept is important and new does NOT mean that we need to start using magical words to describe it. (I am obviously poking fun but I think the point is important). I made some suggestions using Adobe's tools within your document.

Otherwise, I think I gave you my opinions/context/emphasis points last week.

Jim

Sotatercept (Merck & Co., Inc) is a first-in-class activin signaling inhibitor which may improve pulmonary blood flow ~~reverse remodeling changes in the pulmonary arteries and restore vessel patency~~ through inhibiting cellular proliferation, promoting cellular death, and decreasing inflammation in vessel walls.[11] Unlike current therapies, which have at least some direct action as ~~are mainly~~ vasodilators, sotatercept does not directly vasodilate, and its mode of action is clearly different than presently approved drugs ~~has the potential to be a diseasemodifying agent~~. It has been studied as a subcutaneous injection every 3 weeks added on to stable background therapy and a Biologics License Application is expected to be filed with the US Food and Drug Administration in 2023.

My name is [redacted], living in [redacted] and got diagnosed with PAH November 2020 in Germany.
Since diagnosed I got rapidly worse and worse, in December 2022 the doctors told me that Ineed lung transplant, because me medicine wasn't a longterm success, after short amount of time I was not longer responding well to different types of medicines.

In January 2023 I was so lucky to make it in the Zenith study in Hannover, Germany. Since then I'm getting so much better! My NT_ProBNP was going from 1300 to 141. My heart is getting smaller, my current medicine (Tadalafil, Opsumit and Remodulin) are reduced to half doses - and can hopefully be reduced more over the next months.

Since I got Sotatercept my life really improved, I can do a lot more physical, I can clean the house, going for a walk with the dog an so much more. It literally changed my life to the better and I feel much more like myself before diagnosis. Some days I even forget about my illness and feel normal, because I don't have the constant breathlessness.
I'm SO grateful to be part of the study and hoping for that sotatercept will become part of the treatment for PAH soon. The drug is a life changer and need to be approved, so every one who suffers from PAH has the chance to life a better and happier and healthier life.
A life without a death threat. Everyone deserves a life worth living for, and I think Sotatercept is the biggest part of, giving people regardless a chronic illness like PAH the hope for a better and improved life. Sotatercept is the reason why I can dream about a better future again, a longer life.

Sotatercept is the most important drug the world of PAH can get, and people with PAH deserve a drug, that can change their life to the better!

My name is [redacted] and I am a group 1 Pulmonary Arterial Hypertension patient about to turn 40 on July 3rd of this year. My current treatments are subcutaneous Remodulin, Opsumit and Sildenafil. I was diagnosed in the Spring of 2021 while living in Colorado. My life changed drastically after that which included relocating my entire life to a lower elevation in another state and cutting back my work hours leaving me at the poverty line, dependent on Medicaid for the first time in my life.

I have not yet had the opportunity to be a part of any of the Sotatercept clinical trials but the results that other PAH patients are showing with this therapy bring a hope of healing that some of us didn't expect in our lifetime. Although this diagnosis eliminates the possibility of my bearing children, I have so much ambition, passion and life left to live and access to this drug would give me an opportunity to spend as much time as possible with my family and friends. As a single person with limited capacity to work in the career paths I've spent my whole life immersed in, I've been relying on my aging, retired parents for support. Affordability and accessibility to this drug could be an imperative pivot point for myself and others like me. Imagine finding out you had a rare, incurable disease, spending a couple of years wrapping your head around that all while learning a new way of life with painful drug therapies and side effects. Then imagine there was a drug on the horizon, first of it's class, that could turn this around for some of us and give us our lives back! Please, please consider that this is a life or death matter when making your decisions based on cost.

My biggest hope is to be able to support myself once again… if that's a possibility then I will never stop fighting for my health and wellness!

To Whom It May Concern:

I was diagnosed with Pulmonary Arterial Hypertension in on February 5, 2021. The date will never leave my mind. When I was met with that diagnosis, I had never even heard of PAH. The hospital I was at had extremely limited knowledge of the condition, which is why I wasn't even diagnosed with it when I had a week-long hospital admission in December 2020.

For a disease that is so rare and unknown, I can tell you the dates of every major event having to do with my diagnosis because it has become the biggest focus of my life over the last 2.5 years. September 7, 2020, the first day I felt symptomatic to the point where I knew something was wrong. During September-November, my PCP worked closely with me to try and figure out what was going on to no avail. December 3, 2020, I had a nosebleed so massive that it sent me to the hospital. My blood pressure was near stroke level. After four hours, the ER discharged me, and I got in my friend's car and before she even pulled away from the front door, I passed out for 10 minutes. Needless to say, I was readmitted and started in one hospital and was later transferred to another one during my week-long stay. I was discharged thinking I had heart failure and hypertension. So, I lived until February not feeling any real relief. I passed out again in February and was readmitted February 3, 2021. Luckily, I only had a 3 day stay but, in that stay, I was diagnosed with PAH.

After this diagnosis of a disease unknown to me, I Googled my heart out as you could imagine. It terrified me. I kept seeing 2.8 years survival and things about this disease beingterminal. Words and phrases like no cure, progressive, life expectancy, risk, heart failure, and so many more. At the time of my diagnosis, I was 30 years old. I had always envisioned a long life ahead of me with 2.5 kids, a husband, the picket fence, traveling the world, you know the dream. Suddenly, all of that was wiped away. I kept saying words and phrases like hopeless, what's the point, why me, early death, it will kill me, and again, so many more. I went from feeling like I have the possibility of this beautiful life to I have the possibility of dying soon. Talk about a shift for someone who is supposed to be living life in their prime. Later I of course learned that in addition to all those things, I would not be able to ever birth my own child. After consulting a high-risk pregnancy clinic, I wouldn't even be able to go through harvesting my eggs because I had a Pulmonary Embolism in December of 2020, and the risks were too high. My life as I knew it and expected were over.

In June of 2021, I was referred to Vanderbilt's clinic that has PH specialists. Since my treatment began there, overall, I have seen bits of improvement. I earned myself a three-week hospital stay in May of 2022 because I was in such bad shape. It has taken until literally last month (May 2023) to feel like I was getting a good course of treatment. I have tried Sildenafil and Uptravi and my current course of treatment is Tadalafil, Opsumit, and subcutaneous Remodulin. These drugs have literally saved my life. Without them, I truly believe I would not be here today. But all that to say, the treatments feel like a band aid on a bullet hole. They are just that, treatments, not cures. Ultimately, PAH will kill me with the treatments that are available.

It's a bit scary because I'm coming up on that 2.8 years here soon and while I hope, and logically know, that I likely will not be dying in the next 6 months, I so wish there was more hope out there. Sotatercept is that hope. Whenever I read articles about the clinical trials and the results of studies, it actually makes me cry because the people in these trials are offering up their bodies and lives to help the rest of us. And the risk is paying off. 84% of patients on the drug are seeing improvement! That is such an incredible statistic. It gives me so much hope that I can begin to envision a new future for myself. Sure, things might be quite different, but this new breakthrough drug could give me and other PAH patients the opportunity to start just flat-out enjoying life every day without hesitation or restriction. This is the new dream and one that I believe if Sotatercept became available to the larger market is a drug that will make it possible to have dreams and see them through without questioning the what if's.

I urge you to evaluate not only the drug, the clinical trials, the opinions from stakeholders, etc. that you have to evaluate but to also take into consideration the impact to the lives of the PAH patients. Right now, collectively we don't share a lot of hope. But this drug has given this community a sense of hope. Please champion this drug for FDA approval on behalf of all of us and on behalf of all of us being able to have dreams again.

Thank you for your time and the work you are doing.

To whom it may concern,

My daughter has been diagnosed with Pulmonary Arterial Hypertension (PAH) which is considered by the medical community to be a progressive and terminal disease. There is no known cure for PAH so treatment boils down to minimizing the effects of the disease and managing the symptoms. Having PAH severely impacts daily living and existing therapies are at best only a bridge to a time where a cure may be possible. That time may have arrived.

I am writing this letter to voice my support for FDA approval of Sotatercept, which is a new drug to treat PAH. Sotatercept has shown amazing results in clinical trials with more than 84% of the participants showing improvement, with the possibility of reversing some of the damage patients have already suffered. Until Sotatercept was developed, reversal of PAH was considered impossible.

Coping with PAH on a daily basis is extremely difficult. My daughter has endured hospital stay after hospital stay, a number of different pharmaceutical treatments resulting in bouts of nausea, diarrhea, headaches and loss of appetite. She is now receiving her current medication, Remodulin, through a pump that she is attached to twenty-four hours a day. This course of therapy is not a cure, it is simply a stop-gap measure that lets her life get somewhat back to normal in terms of daily living. The last two years have been nothing short of miserable for her with no permanent solution or path to recovery in sight. Sotatercept may be the drug that changes that outlook.

It is clearly understood that developing a new drug is a monumental task and requires a great deal of capital. The market for a drug like Sotatercept is limited to individuals suffering from PAH which dramatically impacts the size of the market for a drug of this nature. However, it is difficult to put a price tag on a new drug that may prolong life for many sufferers of PAH and possibly offer a cure for this disease. PAH affects not only the lungs, but due to restrictions in the pulmonary arteries puts a significant strain on the heart as well. Without some method to reduce the combined effects of these factors, the outlook is dismal. Sotatercept may change all that, but it has to be within the grasp of those suffering from this disease. Return on investment needs to be tempered with the ability to prolong and possibly even save lives. The pricing of Sotatercept cannot put the possibility of a cure out of the reach of those that need it most. It is difficult to put a price on the value of a human life and balance it with the profitability of a corporation. I am in no position to attempt to propose a solution to this issue but pray that this drug will be priced so those that need it most are able to take advantage of the hope that it appears to provide.

Sincerely,

[redacted]

Hope you are well.

I'm [redacted], a 30-year-old male suffering from severe pulmonary arterial hypertension. I'm writing this email to voice my opinion on faster FDA approval of Sotatercept. I'm currently on triple therapy- subq treprostinil, sildenafil and macitentan. I was an active individual working well professionally till 3 years back when my condition deteriorated. I'm currently bedridden and having difficulty in doing my day-to-day activities due to this disease.

The entire PH patient community is watching the trial of Sotatercept with bated breath and we couldn't say how happier we are to know about the positive effects the drug has shown so far.

All the patients across the world are looking forward to the FDA approval and formal launch of Sotatercept. FDA approval is an important moment not just for the patients in USA but patients across the globe as the approvals and launches in countries other than USA get easier once the drug gets FDA approval.

We are hopeful that ICER pushes for a faster FDA approval and a faster launch for Sotatercept along with a lower price range as patients are already on triple therapy.

Happy to provide any more information or participate in information sharing regarding this.

Please get the drug launched asap and help millions of PHigters live their lives normally!

Yours sincerely!

[redacted]

To whom it may concern,

My name is [redacted] and I live in [redacted] and I am a 33 year old, twin mom to 5 year old boys and prior Army military wife. I was diagnosed with idiopathic pulmonary arterial hypertension (PAH) and congestive heart failure in 2018 and was told that without treatment, I would only make it another year, two years at best.

Pulmonary arterial hypertension is a nasty disease that progresses differently in every person. Because of its severity, my condition was emergent and I needed to be put on IV treprostinil right away. The last 5 years have had a lot of ups and downs, and my disease is more progressive than most, even though I look healthy on the outside.

I am currently on triple therapy for my PAH which are subcutaneous treprostinil, tadalafil and ambersentain. I was accepted into a clinical trial with [redacted] for the new Merck drug, Sotatercept in January of 2022. This came at a time when my condition was rocky and my team and I were just starting talks about a double-lung transplant as a last resort to lengthen my life expectancy.

Since diagnosis it's been very hard on our family when it comes to medical costs. Even though my husband is a federal officer, we pay an astronomical amount of money for health insurance and for my medications. PAH meds are some of the most expensive meds on the market. Unfortunately, I have been unable to work a full time job because of clinic visits and hospitalizations, my body just isn't what it used to be. But the worst part of all is that for the last five years, it's been hard to be 100% there for my boys. I want to see them grow up and become men, and I hope to walk them down the aisle to their spouses one day, and Sotatercept could do that for me.

I have been on the drug since November and I am happy to say that for the first time in almost 5 years, we are talking about coming off of pump therapy and my condition is better than ever

before. My last echo results showed that because of the Sotatercept, my heart failure is almost undetectable, I walked further in my six minute walk test and my lung function tests were almost normal. This is huge for the PAH community, many of whom have gotten this diagnosis and the progression has gotten worse too quickly for the current medications to work.
Sotatercept gives this community a sense of hope that it's never had. This drug could eradicate so many heartbreaking moments for PAH patients and the future PHighters could possibly manage it as easy as diabetes without the need for pump therapy. We could live long, happy lives with this medication.

So please, I urge you to consider that when you're making decisions on cost and accessibility. Because approved FDA drugs don't always mean accessible to the general public, and this community is desperate for hope. Sotatecept is that hope.

Thank you for your consideration,
[redacted]

Public comments in scope document- Sotatercept

I am a patient of Idiopathic pulmonary hypertension, WHO FC 11

I live in [redacted]. My condition was diagnosed in 2019 and since then I am on oral therapies of Tadalafil & Macitentan and recently six months ago due to worsening condition, Selexipag was added so I am on a triple oral therapy. My ability to do daily chores had greatly reduced and heart function impaired as a result, every breath I take is noticeable and so difficult to live life like a normal human being.

I have been following up Sotatercept clinical stellar trials for sometimes and the patients who have trialled have seen amazing results in terms of ease of breathing, getting back quality of life, potential longevity and coming off from IV pump, which is so amazing.

It is hard to imagine the life we PAH patients live where every breath is difficult and small tasks which a healthy human do without even thinking about, we get breathless and helpless in performing basic tasks as basic as taking a shower !

Not only the mortality rate is high but also whatever life we are left with is a constant struggle to keep breathing and try to be as independent as we can but every moment of our life we just cannot breathe properly. This affects our personal, emotional, work life as who would like to employ people who find it difficult to perform normal day today tasks of self-care and basic living.

I, wholeheartedly welcome the research done by Merck and co. and trails and efforts put in for so many years to come out with a drug which gives hope to us patients that we also have a right to live and longer and enjoy the gift of God and to be with our loved ones for a longer time and with effective management of this nasty disease which cripples our life and reminds us what we go thru with every breath.

As a member of the public and a patient, experiencing the disease myself, cannot wait to have sotatercept approved by FDA and authorities and be made available to public, patients like me. This is a hope, we sufferers of PAH live on that one day our lives will be better and Sotatercept gives us that hope.

I appeal to the authorities to please support this initiative of Merck and approve the drug ASAP.

June 5, 2023

Comments on behalf of the Pulmonary Hypertension Association

RE: ICER Draft Background and Scope, Sotatercept for Pulmonary Arterial Hypertension

The Pulmonary Hypertension Association (PHA) is the country's leading PH organization. PHA's mission is to extend and improve the lives of those affected by PH. PHA achieves this by connecting and working together with the entire PH community of patients, families, health care professionals and researchers. The organization supports more than 150 patient support groups; a robust national continuing medical education program; a PH clinical program accreditation initiative; and a national observational patient registry.

PHA appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft background and scope related to sotatercept for treatment of pulmonary arterial hypertension (PAH). Comments are organized below according to the segment of the draft scope and background document to which they relate.

Background

PHA commends the ICER reviewers involved in the Sotatercept review for their commitment to learning about the clinical and quality of life impacts of PAH, a progressive, life-threatening condition with significant, sustained clinical, economic and psychosocial impacts.

ICER's draft background and scope document states that "Black persons may have a higher risk of developing PAH and are overrepresented in registries compared to the general population." However, enrollment in the Pulmonary Hypertension Association Registry (PHAR) does not reflect an this "overrepresentation." Enrollment in PHAR is 14% Black or African American, slightly below the Pew Research Center estimate that of the general U.S. population, 14.2% are Black[1].

PHA encourages ICER to clarify background information related to correlations between race and pulmonary hypertension diagnosis, treatment, survival and registry enrollment.

Stakeholder Input

The Stakeholder Input section of the draft sotatercept scoping document lacks a clear picture of why diagnosis and treatment of pulmonary hypertension is delayed and understates the impact of medication side effects on patients' lives.

Delayed Diagnosis

The draft scoping document states, "Because symptoms can initially be mild, there is often a delay both in seeking medical attention and in diagnosis, which can impact both survival and quality of life."

While it is accurate that delayed diagnosis significantly impacts the effectiveness of treatment for both survival and quality of life, the reasons for delayed diagnosis are **generalized** symptoms, ranging from mild to quite severe, that are misdiagnosed by health care professionals. Common

symptoms of PH include shortness of breath and fatigue. Individuals with even severe symptoms frequently do not receive the appropriate testing or referral to expert care. PAH patients may struggle for years with incorrect diagnoses, including but not limited to asthma, COPD and anxiety. More than 70% of PAH patients are functional class III or IV by the time they receive an accurate diagnosis[2]. Disease progression that occurs during this prolonged misdiagnosis period may not be reversable even after appropriate therapy is initiated.

In a related occurrence, patients who are not seen by health care professionals with expertise in pulmonary hypertension may be under-treated, failing to receive advanced therapy options even when their PAH has progressed[3].

Medication Side Effects
PHA is pleased to see medication side effects and mode of administration considered in the draft scoping document as components of PAH that significantly impact patients' lives. In fact, PHA believes that the scoping document, while factually accurate, understates the life-altering impact of side effects and administration burden for current PAH therapies.

The draft scoping document states, "Treatments for PAH are helpful for symptoms but can come with significant side effects such as pain, dizziness, and swelling. Mode of delivery of medications can have an impact on quality of life …"

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 side effects, including but not limited to pain and GI effects, can be debilitating and keep patients homebound even when the patient's PAH-specific symptoms have improved.

Scope of Clinical Evidence Review
Outcomes
PHA encourages consideration of the need for supplemental oxygen as an outcome of interest. Many PAH patients have been prescribed supplemental oxygen in addition to pharmacologic treatments. Prescribed oxygen use varies by patient and ranges from using oxygen only at night or during exertion to continuous use. The prescribed flow rate also varies, with many PAH patients requiring a high flow rate that can not be adequately met by a portable oxygen concentrator.

A prescription for high-flow oxygen is challenging to have filled even when covered by insurance, and the equipment necessary to maintain a high flow is often heavy and bulky. Combined with extremely limited battery life (two hours or less) for some equipment, PAH patients are often homebound because of the limitations of their oxygen equipment rather than the symptoms of their disease. Therefore, reducing the need for oxygen is an important outcome for many individuals with PAH. Reduced need for oxygen could be measured based on flow rate (decreased liters per minute to maintain saturation) and/or hours of use needed per day.

Potential Other Benefits and Contextual Considerations

Categories of Contextual Considerations
In Table 1.2: Categories of Contextual Considerations and Potential Other Benefits, PHA recommends the inclusion of quality of life as both a contextual consideration and a potential other benefit due to the significant burden of the disease and current therapy options as well as the significant opportunity presented by sotatercept.

Scope of Comparative Value Analysis
Within the scope of comparative value analysis, PHA would like to draw attention to the potential for sotatercept to be disease modifying. ICER's modeling for health care costs should be within the context of the fact that current treatments maintain health or delay disease progression. A disease modifying therapy could reduce long-term healthcare costs, especially for those who are diagnosed and treated early.

In addition, PHA advocates for robust access to all PAH therapies so that treatment can be driven by clinical judgement and the patient clinician relationship. Addition of a new therapy to the PAH market should not reduce access to other therapies, because different patients tolerate each therapy combination differently. Optimal care is obtained when clinicians can choose from the full range of PAH therapies with the confidence that the most appropriate therapies for each patient will be accessible to that individual.

Identification of Low-Value Services
PHA recommends extreme caution and careful, multi-factorial analysis on ICER's part in considering potential low-value services.

Leadership of PHA's Pulmonary Hypertension Care Centers accreditation program (PHCC) have identified accreditation criteria that leverage a collaborative care model to maximize patient outcomes. Underestimating the value of this multi-disciplinary collaborative care model could lead to an unintended declines in length and quality of live for individuals with PAH.

In conclusion, PHA recommends the following adjustments to ICER's draft background and scope for review of sotatercept for pulmonary hypertension:

- Clarified language about correlations between race and pulmonary hypertension diagnosis, treatment, survival and registry enrollment.
- Modified discussion of delayed diagnosis to account for under recognition of and insufficient response to the disease by health care professionals.
- Expanded discussion of the debilitating impact of medication side effects.
- Addition of the need for supplemental oxygen as an outcome of interest.
- Inclusion of quality of life as both a contextual consideration and potential other benefit.
- Recognition of the unique context of sotatercept as a potentially disease modifying therapy.
- Increased emphasis on robust access to all PAH therapies and treatment driven by expert clinical judgement.
- Extreme caution and multi-factorial analysis when considering potential low-value services.

References

1. Moslimani M, Tamir C, et al. (2023, March 2). *Facts about the U.S. Black population.* Pew Research Center. https://www.pewresearch.org/social-trends/fact-sheet/facts-about-the-us-black-population/

2. Pi H, Kosanovich CM, Handen A, et al. Outcomes of pulmonary arterial hypertension are improved in a specialty care center. *CHEST.* 2020. Jul;158(1):330-340.

3. Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL registry. *CHEST.* 2011. Jul; 140(1):19-26.

Hello,

my name is [redacted] and I'm writing to you as a patient of Pulmonary Arterial Hypertension. I was diagnosed 6 years ago and the only treatment I can have at this moment is Veletri, an intravenous medication 24/7 by pump and a hickman catheter.

As you can imagine, my quality of life has been tremendously changed, I'm 38 and psychologically I've been broken with so many losts (work, health, impossibility of pregnancy, acceptance of my new reality and body...).

I'm sorry for telling you all this information, but what I want to expose is the need of a new medication so powerful as Sotartecept for sick people as me who are dependent on a pump. Sotatercept can change our lives and, as my doctor says, Sotartecept would give me the chance to have another option before transplant, which can be the end sadly.

I really thank you for your time and attention, I beg you to consider how we need to have this drug disposable and as soon as possible, cause time doesn't help us.

Best regards.
[redacted]

My name is [redacted] and I am a 45 year old patient with pulmonary arterial hypertension group 1. My current treatments are IV remodulin, opsumit, tadalafil, and I am participating in a clinical trial at University of Texas Southwestern Medical Center in Dallas Texas. This medication is inhaled riociguat. I was diagnosed in August of 2020 although I was quite sick shortly after having my fourth child at 40 years old. My youngest child is only 5 now and my biggest fear is not living to her 18th birthday. At least. You see I am her only safe and secure parent despite being terminally ill. I am desperate for more time. These studies for Sotatercept have given us a new hope for more time with our families. I pray to see the same results as some people participating in the trials. Please, this is life and death for many of us. Please consider us when making decisions based on cost. Many, if not all of us are on fixed incomes and can barely afford to live as it is. My hope is that Sotatercept can give me the opportunity to work again. I worked 18 years as a long term care nurse before I became sick. In fact I worked for three years with heart failure because I have children that I alone am responsible for. And I would give anything to be able to work as a nurse and contribute to the health care community. I was a very capable and competent nurse. I know my skills are needed. I appreciate your time. And thank you for all you do for the pulmonary hypertension community. We are a tight bit group of fighters who deserve hope.