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A belgian consensus on sotatercept for the treatment of pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a rare disease affecting the small pulmonary vessels, ultimately leading to right ventricular failure and death. Current treatment options target 3 different pathways (endothelin, nitric oxide/cGMP and prostacyclin pathways). Despite their demonstrated efficacy, these therapies (commonly used in combination) do not cure the disease which is why novel pathways beyond the traditional "big three" are being developed. Sotatercept is a ligand trap for multiple proteins within the TGF-β superfamily that was recently approved in the US for the treatment of PAH. Unlike currently available therapies, sotatercept has the potential to act as an anti-remodeling agent rather than a vasodilator. The safety and efficacy of subcutaneous sotatercept have been established in two multicenter, placebo-controlled randomized-controlled trials. The compound has been shown to consistently improve a variety of measurable endpoints, including exercise capacity, hemodynamics, quality of life and delay of clinical worsening. The drug appears to have an acceptable safety profile, although it is associated with an increased risk in developing telangiectasia and biological changes affecting platelet counts and hemoglobin. This manuscript reviews the current evidence on subcutaneous sotatercept and provides a Belgian perspective on its place in the future treatment strategy for PAH.

Introduction – where is treatment for PAH in 2024?

Pulmonary arterial hypertension (PAH) is a severe progressive disease affecting the small pulmonary vessels, characterized by sustained elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) caused by vascular remodeling[1]. PAH is also a clinical syndrome of dyspnea and fatigue, ultimately leading to right ventricular (RV) failure and premature death. Over the past 30 years, major progresses have been made in understanding the pathobiology of PAH, leading to important advances in therapy[2]. In brief, the development of PAH involves multiple mechanisms (including genetic changes, inflammation, thrombosis, endothelial dysfunction, cell proliferation and fibrosis) leading to pulmonary vascular remodeling. In other words, the current understanding of pathobiology is no longer seen as a simple imbalance between vasoconstriction and vasodilation[3]. Currently available therapies target three main dysfunctional pathways: 1) endothelin receptor antagonists (ERAs: ambrisentan, bosentan, macitentan) block the negative effect of endothelin-1, which is increased in PAH; 2) prostacyclin analogues (epoprostenol, Treprostinil, beraprost) and/or prostacyclin receptor agonists (selexipag) aim to restore the vasodilatory effect of prostacyclin; 3) phosphodiesterase-5 inhibitors (PDE5i: tadalafil, sildenafil) and soluble guanylate cyclase stimulators (sGCS: riociguat) restore the nitric oxide (NO)/cyclic GMP signaling in PAH. These three major pathways are commonly targeted in combination, at time of diagnosis and during follow-up[1]. Despite these advances, PAH remains an incurable disease with a significant impact on quality of life and a poor prognosis[1].

A growing interest in targeting novel pathways has greatly accelerated the search for a new treatment. Sotatercept is the latest addition to the treatment armamentarium for PAH and has recently been approved by the United States Food and Drug Administration (FDA) by the end of March 2024, pending approval by the European Medical Agency (EMA).

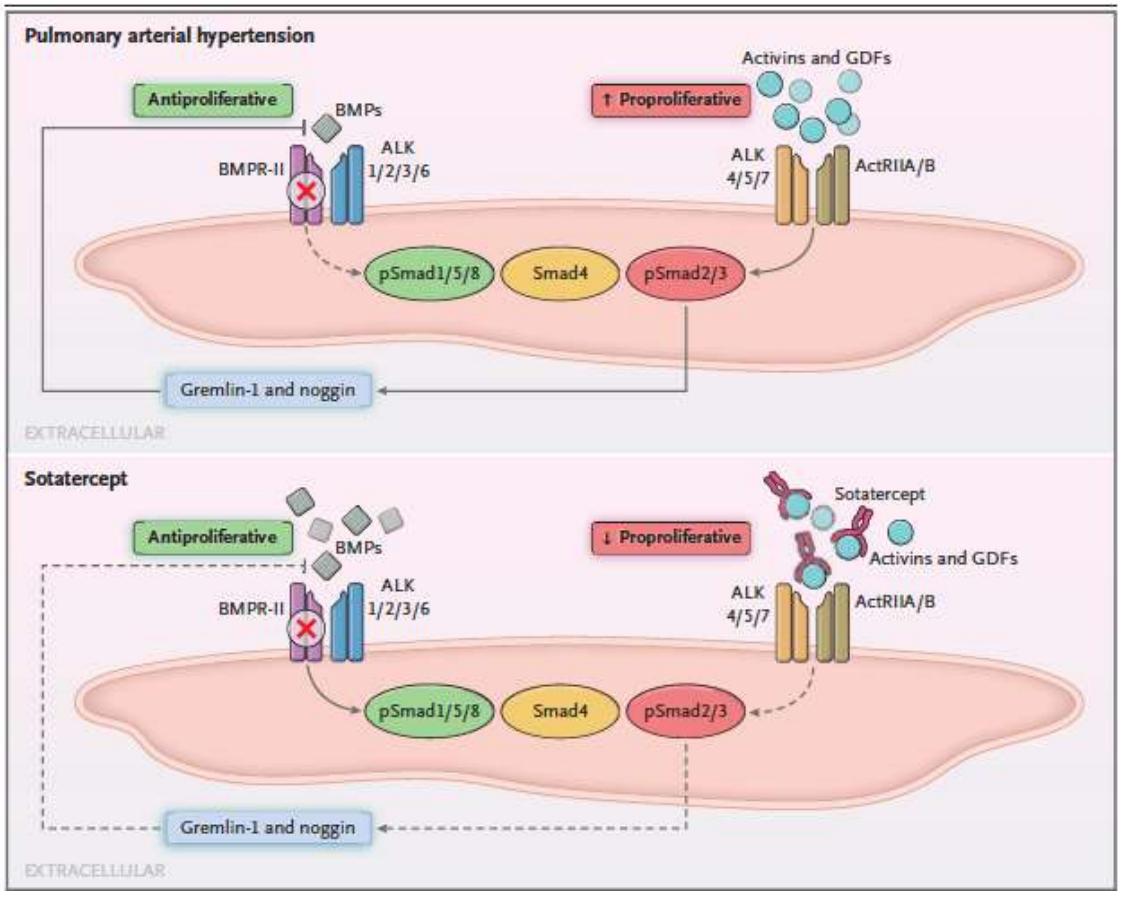
This article aims to briefly review the clinical evidence for sotatercept and provide a Belgian perspective on the place of the drug in the current PAH treatment algorithm.

Sotatercept: a breakthrough in the treatment of PAH

Recent research identified the role of altered signaling by members of the transforming growth factor β (TGFβ) superfamily in the development of PAH[3]. The latter includes bone morphogenic

protein receptor type II (BMPR2, one of the first mutation identified as a genetic signatures of PAH), activin receptor type II A (ActRIIA), and the ActRIIA ligands activin A, activin B, growth differentiation factor 8 (GDF8) and GDF11[4]. An imbalance in anti-proliferative signaling through ActRIIA leads to hyperproliferation and further vascular remodeling[5].

Sotatercept is a novel, first-in-class fusion protein that binds to ligands of the TGFβ superfamily, thereby rebalancing the pro- and anti-proliferative ActRII2A/B signaling[6]. As such, it targets a pathogenic pathway that is not addressed by currently approved PAH therapies, which mostly target endothelial-derived proliferative mechanisms. The mechanism of action of sotatercept is summarized in *figure 1*.



Legend of figure 1 (after reference 6):

Sotatercept acts to sequester excess ActRIIA ligands, thereby reducing ActRIIA–Smad2/3 signaling to rebalance growth-promoting and growth-inhibiting signaling. ALK denotes activin receptor–like kinase.

Abbreviations: ActRIIA = activin receptor type II A; ALK = activin receptor-like kinase; BMPs = bone morphogenic proteins; BMPR-II = bone morphogenic protein receptor type II; GDF = growth differentiation factor; (p)SMAD = (phosphorylated) suppressor of mothers against decapentaplegic

The efficacy and safety of sotatercept was first evaluated in PULSAR (NCT03496207), a Phase 2, multicenter, randomized, placebo-controlled, double-blind study[6]. In this study, patients with PAH — idiopathic, heritable or associated with connective tissue disease or corrected congenital heart disease — who remained symptomatic (NYHA II-III) on standard PAH therapy were randomized in a 1:1:1 ratio to receive subcutaneous (SC) sotatercept at a dose of 0.3 or 0.7 mg per kilogram of body weight every 3 weeks or placebo for 24 weeks. Safety and efficacy were evaluated every 3 weeks through week 24 of the placebo-controlled phase. Similar to previous Phase 2 studies, the primary endpoint was the change from baseline to week 24 in PVR. The study population consisted of 106 adults with similar characteristics in the 3 groups. In contrast to previous studies, the time from diagnosis was long (7.7±5.6 years, mean±SD), 56% were on triple therapy for PAH and 37% were receiving parenteral prostacyclin. Despite intensive treatment, patients presented with severely impaired hemodynamics, a mean six-minute walk distance (6MWD) of less than 400 m, and an elevated N-terminal pro-brain natriuretic peptide (NT-proBNP). Compared to placebo, sotatercept significantly decreased PVR at both the 0.3 mg/kg dose (–162.2±33.3 dyn·sec·cm−5 P = 0.003) and the 0.7 mg.kg dose (–255.9±29.6 P<0.001). 6MWD was also improved by +29.4 m (95% CI, 3.8 to 55.0) and + 21.4 m (95% CI, −2.8 to 45.7) in the 0.3 and 0.7 mg/kg groups, respectively, compared to placebo. Other improvements in secondary endpoints were also observed, including a more significant reduction in NT-proBNP. Regarding safety, thrombocytopenia and increased Hb levels were the most common adverse events observed in the treated group. Interestingly, sotatercept was also associated with an improvement in pulmonary artery (PA) compliance and RV/PA coupling[7]. After 24 weeks, 97 patients continued in the open-label extension of the study, confirming the durability of effect and the safety profile of sotatercept observed in PULSAR[8].

The pivotal trial STELLAR (NCT04576988) was a Phase 3, multicenter, double-blind, study in adults with PAH with similar characteristics to PULSAR[9]. Patients on background therapy were randomized 1:1 to receive placebo or SC sotatercept at a starting dose of 0.3 mg/kg followed by a target dose of 0.7 mg/kg every 3 weeks. Similar to most pivotal trials in PAH, the primary endpoint was the change from baseline at week 24 in the 6MWD. In addition, nine secondary endpoints were tested hierarchically in the following order: multicomponent improvement, change in PVR, change in NT-proBNP level, improvement in WHO functional class (FC), time to death or clinical worsening, French risk score, and changes in a PAH-specific patient-related

outcome (PRO) called the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT). With the exception of mortality-morbidity outcome, all measures were assessed at week 24. The study population (N=163 sotatercept and N=160 placebo) had remarkably similar characteristics to the PULSAR population. The time from diagnosis was 8.8±7.0 years, 61.3% were on triple background therapy with 39% receiving parenteral prostacyclin and there was an almost even split between WHO FC II and III (48.6 and 51.4% respectively). Compared to placebo, sotatercept improved 6MWD after 24 weeks (+40.8 m (95% CI, 27.5 to 54.1); P<0.001). Also of note was the significant improvement in the first eight secondary endpoints, while the PAH-SYMPACT Cognitive–Emotional Impacts domain score did not improve. Notably, more patients in the active arm improved (1st hierarchical secondary endpoint) and fewer patients experienced a clinical worsening event (5th hierarchical secondary endpoint). Adverse events that occurred more frequently with sotatercept (41.1%) compared to placebo (25.6%) included bleeding (21.5% vs 12.5%), epistaxis (12.3% vs 1.9%), dizziness (10.4% vs 1.9%), telangiectasia (10.4% vs 3.1%, thrombocytopenia (6.1% vs 2.5%), increased hemoglobin levels (5.5% vs 0%) and increased blood pressure (3.7% vs 0.6%). However, the discontinuation rate was lower in the sotatercept group (1.8% vs. 6.2%).

Therefore, the data from PULSAR and STELLAR support the use of sotatercept for the treatment of PAH with a consistent benefit across the spectrum of clinically relevant endpoints, offering an improvement in quality of life and a reduced risk of disease progression, together with a reassuring safety profile.

Clinical development of the drug continues with two ongoing studies evaluating the benefit of sotatercept in reducing the risk of clinical worsening in recently diagnosed patients (HYPERION, NCT04811092) and in patients with advanced disease (ZENITH, NCT04896008).

A Belgian perspective on sotatercept

Historically, Belgium has been at the forefront of PAH drug development from the very beginning. This has led, at least in part, to the approval of almost all available treatment options worldwide. In our country, patients with PAH can benefit from highly specialized care throughout Belgium, in line with international recommendations, including parenteral prostacyclin and transplantation in dedicated centers. Naturally, a group of physicians (pulmonologists and cardiologists) involved in the management of P(A)H gathered to provide

a country-specific perspective on the use of sotatercept in Belgium. The following comments reflect a consensus statement amongst PH specialists.

As a background, it is important to highlight that PULSAR and STELLAR enrolled patients who were young (mean age 50 years), highly prevalent with a time from diagnosis of 8-9 years and a large majority receiving triple therapy (60%). Notably, the proportion of patients receiving parenteral prostacyclin was 39%, well above registry data suggesting that 15-20% of patients receive intravenous treatment[10]. Over the years, the patient profile has changed with a significant increase in age and burden of cardiorespiratory comorbidities[1]. This has been taken into account in the current ESC/ERS guidelines for PAH. However, based on the mechanism of action of sotatercept, neither age nor comorbidities are expected to affect treatment efficacy or safety. In addition, the ongoing trial CADENCE (NCT04945460) is expected to provide further insight into the effect of sotatercept in patients with combined post- and precapillary pulmonary hypertension associated with heart failure with preserved ejection fraction (HFpEF). Although the EMA labeling remains to be disclosed, the current FDA labeling states that sotatercept is indicated for "adult patients with PAH in WHO functional class II or III who have been on stable monotherapy, double or triple PAH therapy for at least 3 months". These preliminary remarks led the panel of Belgian PH specialists to consider the following

- In general, access to this innovative therapy should not be too restrictive. More specifically, the lack of specific data in patients with comorbidities should not exclude this patient phenotype, as the benefits outweigh the risks. Based on this, a rough assessment suggests that approximately 50% of the Belgian PAH patient cohort could benefit from sotatercept therapy.
- Nevertheless, the panel agrees that the effect of therapy should be closely monitored, and real-world data should be further collected, in line with proposed future directions[2].

Pregnancy and breast-feeding are considered the only absolute contraindications to treatment with sotatercept. Based on the drug's safety profile, the panel still believes that extra attention should be paid when considering sotatercept in patients with a high burden of comorbidities that affect exercise capacity and survival independently of pulmonary vascular disease. Therapy should be considered and closely monitored in patients with: 1) hemoglobin values higher than the upper limit of normal — this is particularly relevant in patients with

congenital heart disease and Eisenmenger syndrome (ES) and secondary polycythemia (see below); 2) systemic hypertension; 3) thrombocytopenia with platelet count <75.000; 4) clinical signs of hereditary hemorrhagic telangiectasia (formerly Rendu-Osler disease) or heterozygous ALK1 or ENG mutations, because sotatercept is associated with an increased risk to develop telangiectasia — patients with these characteristics may be treated with the lowest dose of sotatercept until more safety data are acquired. There is no data on the use of sotatercept in porto-pulmonary hypertension, chronic liver disease and patients with ES. Although it is uncertain whether these indications will be included in the labeling, it is felt that an extra level of caution should be applied in these indications. Sotatercept should not be used in patients with ES who undergo occasional phlebotomy. There is no published data on concomitant use of sotatercept with anticoagulants and antiplatelet agents. The investigator's brochure reports that 18 participants in the clinical development program had a serious bleeding event; half were receiving an anticoagulant and a prostacyclin analog. Caution is therefore recommended in such situation.

Guidance for the use of sotatercept in practice

The Panel believes that the use of sotatercept should not be restricted to centers with access to parenteral prostacyclin. However, the following is recommended:

- Specialist nurses should be involved in the initial administration of the drug, and in the education of patients and home care services.
- A 24-hour helpline should be available for questions regarding dose, site of administration, drug preparation, and side effects.
- Peer-to-peer collaboration between centers with and without previous experience in the use of sotatercept is strongly encouraged.
- In the event of dose reduction or discontinuation due to adverse reactions, the patient should be evaluated by the prescribing physician at the time of the next injection.
- In the absence of clinical or hemodynamic benefit after > 6 months of treatment with sotatercept in patients already on triple therapy for PAH, withholding therapy may be considered and inclusion in studies exploring other pathways may be evaluated.

- Patient representatives on the panel emphasize the importance of tailoring the mode of administration, i.e. self-administration vs. home-based nurse support, to the specific needs of the patient.

In addition, the Panel believes that a greater collaboration between centers would be of significant benefit to patients.

- The Panel strongly supports the collection of data in a prospective registry to provide real-world data on specific subgroups of patients. As a result, all PH specialists are willing to reactivate the concept of a Institute of Public Health (Sciensano)/ National Institute for Health and Disability Insurance (INAMI-RIZIV)/PH centers/Pharma joint registry.
- A monthly multicenter, multidisciplinary team meeting to discuss various issues (difficult cases, indication of sotatercept and parenteral prostacyclin, side effects of PAH drugs, reimbursement issues) would be of added value.

A look into the future

The PH community (including partners from industry, patient advocacy groups and regulatory authorities) has worked tirelessly to bring a novel treatment to PAH patients. Sotatercept is a more than welcome addition to the current treatment options as a 4th pilar of therapy. Although evidence gaps remain to be filled, the Belgian PH specialists provide an updated treatment algorithm that puts the place of this new treatment in perspective (*figure 2*). PAH risk assessment remains an important step in finding the best treatment for everyone. It is useful not only at baseline, but also at regular follow-up[1]. Data are lacking to support an indication of sotatercept at the time of diagnosis, pending the results of the HYPERION trial. Therefore, the drug is considered as an add-on to background therapy in patients with persistent symptoms and not low-risk profile at initial follow-up.

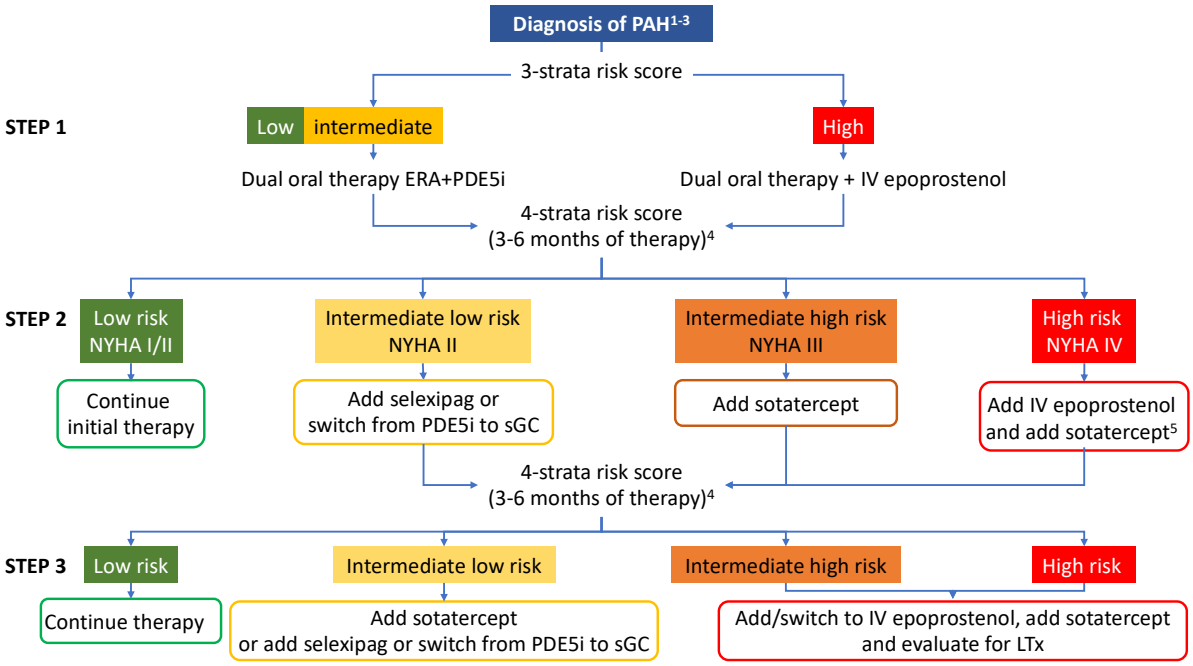


Figure 2: Proposed algorithm for the use of sotatercept in Belgium

1. Efficacy established in idiopathic PAH, heritable PAH, PAH associated with systemic sclerosis, or PAH associated with corrected CHD, all with few cardiopulmonary comorbidities (mean age 48-50 years)
2. Patient preferences should be considered at every step
3. Patients should be considered for inclusion in a study with a novel agent when appropriate
4. Patients should be reassessed sooner in case of deterioration or clinical event
5. Add sotatercept after reaching maximal tolerated dose of epoprostenol

Despite the higher cost compared to older therapies, sotatercept is positioned as step 2 in patients with intermediate-high and high risk because of low 1-, 3- and 5-year survival rates averaging 81-91%, 50-63%, 31-47% and 65-78%, 28-48%, 13-33%, respectively.

Abbreviations: ERA = endothelin receptor antagonist; IV = intravenous; LTx = lung transplantation; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase 5 inhibitor; sGC = soluble guanylate cyclase stimulator

Disclosures

JLV reports consultant and speaker fees from Merck/MSD in the context of the submitted work, and consultant fees from Aerovate, GossamerBio, Insmed, Janssen, Pulmovant and United Therapeutics outside of the submitted work.
MD reports speaker and consultant fees from Ferrer, Gossamer, Janssen, and MSD outside the submitted work, and all paid to her institution.

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