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# Sotatercept: A Novel drug to the manage Pulmonary Arterial Hypertension - Mechanistic Perspectives and Clinical Implications?

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**Abbreviations List :**

**6MWD** Six-Minute Walk Distance

**ActRIIA** Activin Receptor Type IIA

**ALK** Activin Receptor-Like Kinase

**BMP** Bone Morphogenetic Protein

**BMPR2** Bone Morphogenetic Protein Receptor Type II

**CTD-PAH** Connective Tissue Disease-Associated Pulmonary Arterial Hypertension

**ERA** Endothelin Receptor Antagonist

**ET-1** Endothelin-1

**FC** Functional Classification

**GDF** Growth Differentiation Factor

**HPAH** Heritable Pulmonary Arterial Hypertension

**IgG1** Immunoglobulin G1

**IP** Prostacyclin (receptor)

**IPAH** Idiopathic Pulmonary Arterial Hypertension

**mPAP** Mean Pulmonary Arterial Pressure

**NO** Nitric Oxide

**NT-proBNP** N-terminal pro-B-type Natriuretic Peptide

**OLE** Open-Label Extension

**PAH** Pulmonary Arterial Hypertension

**PASMC** Pulmonary Arterial Smooth Muscle Cell

**PAWP** Pulmonary Arterial Wedge Pressure

**PDGF** Platelet-Derived Growth Factor

**PDE5** Phosphodiesterase Type-5

**$PGI_2$** Prostacyclin

**PH** Pulmonary Hypertension

**PVR** Pulmonary Vascular Resistance

**RV** Right Ventricular

**sGC** Soluble Guanylate Cyclase

**TGF-β** Transforming Growth Factor-Beta

**WHO** World Health Organization

# 1. Introduction to Pulmonary Arterial Hypertension (PAH) :

## 1.1 Definition of Pulmonary Hypertension PH:

Pulmonary hypertension encompasses a group of life-threatening conditions with a common feature of an elevated blood pressure translated by a mean pulmonary arterial pressure (mPAP) >20 mmHg in the arteries carrying blood from right ventricle to the lungs, leading often to right heart failure[1].

Pulmonary hypertension is generally classified using hemodynamic characteristics, from which we can mention three key parameters, mPAP ( > 20 in all PH), PVR (pulmonary vascular resistance) which is an indication of the state of blood flow in pulmonary arteries, and PWAP ( Pulmonary wedge arterial pressure) measured by left heart catherisation that reflects indirectly blood volume at the end of diastole thus the function of the left heart[1].

These parameters allow us to differentiate between precapillary PH ( mPAP > 20 mmHg and PWAP < 15 mmHg and PVR > 2 Wood units ) where we can exclude left heart ventricule involvment in the disease and postcapillary PH (PWAP > 15 mmHg) where the main cause is left heart disfunction ( further confirmed by echography [2]) table 1.

| Definition | Haemodynamic charcteristics |
|---|---|
| PH | mPAP >20 mmHg |
| Pre-capillary PH | mPAP >20 mmHg<br>PAWP ≤15 mmHg<br>PVR >2 WU |
| Post-Capillary PH | mPAP >20 mmHg<br>PAWP >15 mmHg<br>PVR ≤2 WU |
| Combined PH | mPAP >20 mmHg<br>PAWP >15 mmHg<br>PVR >2 WU |

*Table 1 Haemodynamic definitions of pulmonary hypertension*

It is also crucial to differentiate PH into 5 clinical groupes that share more or less the physiopathology and hemodynamic characteristics and clinical presentation and treatment plans.

They are classified by World Health Organization into 5 groups [3]:

**Group 1: Pulmonary Arterial Hypertension (PAH)**. This group includes various forms such as idiopathic PAH, heritable PAH, and PAH associated with connective tissue disease, congenital heart disease, or certain drugs and toxins. This thesis will focus on this group.

**Group 2: PH due to left heart disease.** This is the most common cause of PH, secondary to conditions like left ventricular systolic or diastolic dysfunction or valvular heart disease.

**Group 3: PH due to lung diseases and/or hypoxia**. This includes PH associated with chronic obstructive pulmonary disease (COPD), interstitial lung disease, or sleep breathing disorders.

**Group 4: PH due to pulmonary artery obstructions.** The primary cause in this group is chronic thromboembolic pulmonary hypertension (CTEPH), where blood clots obstruct the pulmonary arteries.

**Group 5: PH with unclear and/or multifactorial mechanisms.** This group includes PH associated with hematological disorders, systemic disorders like sarcoidosis, and metabolic disorders.

Ph leads in most cases due to several factors to vascular remodelling of lungs circulation system such as hypertrophy and hyperplasia of the intima and adventitia, leading to an impaired capacity of production of nitric oxide an important vasodilator and an increase in the release of endothelin-1 which is in turn a vasoconstrictor in combination with the proliferation of the smooth muscle cells in response to growth factors, all of this combined with fibrosis and inflammation we have a general recipe that leads to a reduction in vascular radius and response ( Figure 1 ) and thus a higher pressure and afterload (Pressure to be surmounted for the blood to be pumped) in the right heart ventricle , leading generally if left untreated or even after treatment progressively to a fatal ending [4,5].

The treatment for PH depends heavily on the cause and the type of this condition, we are going to focus on the precapillary hypertension specifically PAH (pulmonary arterial hypertension or PH group 1 ), that even with today's recommendations and treatments that usually are only delaying the progress of the condition and not curative by nature, such as nitric oxide boosters ( PDE-5 inhibitors ) and endothelin receptors antagonists and prostacyclin antagonists [6] remain hard to deal with, thus the importance of understanding

the molecular physiopathology and mechanism behind this condition is crucial to developing targeted and efficient treatments in reversing this condition, leading consequently to the birth of targeted disease reversing drugs such as Sotatercept, a novel fusion protein [7] .

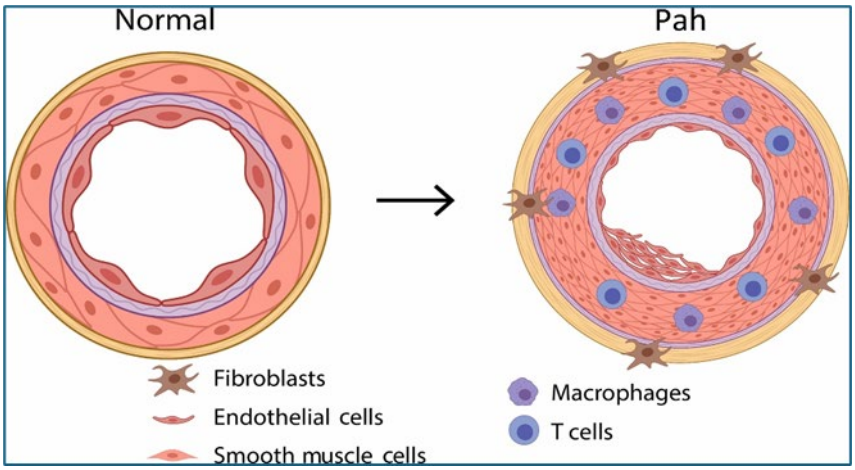


*Figure 1: blood arteriole radius in normal patient vs PAH patients [8]*

## 2 Pulmonary arterial hypertension :

PAH is a Group 1 PH defined as any patients having percapillary hypersention hemodynamic values : mPAP > 20mmHg, PAWP < 15 mmHg, PVR > 2 WU, in the absence of any other CTEPH (Chronic Thromboembolic Pulmonary Hypertension) or PH associated with lung disease [9], PAH is a rare disease poteintially fatal leading generally to modifications and remodelling of the vascular systeme, increasing it's resistance and worsening the state of the patient gradually eventually leading to right heart failuar [9], PAH is also subdivided into several subgroups that differ by their origin, the majoritiy of them being hereditatry due to one or several gene mutations or idiopathic, also we can note PAH caused by drugs and toxins (Table 3), or it can be secondary to underlying conditions such as connective tissue disease, HIV infection, and portal hypertension, congenital heart disease, or Schistosomiasis (2) [10].

It is also important to rank PAH by severety to asses mortality and treatment options.

All pulmonary hypertensions are also calssified by severity in relation to function, called functional classification of pulmonary hypertension, class I being no showing of symptoms at rest or while active, and class II symptoms showing while doing intense activities such as rock climbing and class III showing no symptoms at rest but struggling when doing simple chores, and the most severe class , class IV having shown symptomps even at rest [11] ( Table 3 Functional classification of PH ).

*Table 2 Functional classification of PH [11]*

| Functional Class | Description |
|---|---|
| Class I | I have pulmonary hypertension, but my physical activity is not limited. I can do my day-to-day physical activity (e.g., household tasks, go to work, go to the store) and my usual exercise without getting short of breath or feeling tired, experiencing chest pains, or fainting. |
| Class II | I have pulmonary hypertension and my physical activity is slightly limited. I feel comfortable at rest. I can do my day-to-day physical activity (e.g., household tasks, go to work, go to the store), but it makes me feel short of breath, tired, have chest pains, or faint. |
| Class III | I have pulmonary hypertension and my physical activity is noticeably limited. I feel comfortable at rest. I can do the type of physical activity I have to do on a day-to-day basis (e.g., bathing, dressing, preparing meals), but it makes me feel short of breath, tired, or faint. |
| Class IV | I have pulmonary hypertension, and almost any physical activity makes me feel short of breath, tired, have chest pains, or nearly faint. I frequently experience swollen ankles. I may have a bloated stomach. I may get short of breath or tired even when resting |

*Table 3 Drugs and toxins responsible for inducing PAH [9]*

| Definite association | Possible association |
|---|---|
| Aminorex, Benfluorex, Dasatinib, Dexfenfluramine, Fenfluramine, Methamphetamines, Toxic rapeseed oil | Alkylating agents (cyclophosphamide, mitomycin C), Amphetamines, Bosutinib, Cocaine, Diazoxide, Direct-acting antiviral agents against hepatitis C virus (sofosbuvir), Indirubin (Chinese herb Qing-Dai), Interferon alpha and beta, Leflunomide, L-tryptophan, Phenylpropanolamine, Ponatinib, Solvents (trichloroethylene), St John's Wort |

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## 2.1 Epidemiology :

**Prevalence:** it varies a lot depending on the region, some studies have reported 0.4 per 100000 persons from the centre of French children, while others up to 15 per 100000 during an Australian study of a large database. The average being 3 cases of PAH per 100000 from 12 different studies using RHC mean of diagnosis[12,13] (Figure 2 Prevalence of PAH ).

**Incidence:** it was reported from as low as 0.008 cases per 100000 person-years, to up to 1.4 cases per 100000 person-years, the average cases per 100000 person-years was about 0.4 [12,13]

**Demographic and risk factors:** PAH is noticeably higher in female patients with a ratio of 2.3:1 in young patient, this ratio seems to lower as age increase, reaching 1.2:1 in old patients ( > 75 years old ) [13].

It is also important to note that in patients with CTD-PAH female to male ratio is much higher (9:1), and is a major cause of fatality [13], while CTD-PAH was predominantly in older patients[13].

Some notable risk factors include patients with systemic sclerosis, BMPR2 mutation carriers, or having a first-degree relative with PAH and patients undergoing liver transplantation[9]

**Mortality:** in a meta-analysis study, it was deduced that the fatality rate of PAH functional class (FC) I and II is about 7% for the first year, that then increases dramatically to 22% after 3 years previously thought to be of a lower percentage [14], and for FC III and IV is about 19% for the first year of diagnosis and 45.2% after 3 years, which substantially higher and poses a major threat to the patient [14].

## 2.2 Clinical presentation of PAH:

Common symptoms of PAH are only apparent once the condition worsens and develops to FC II or above, some of the symptoms include[15]:

- Shortness of breath, especially after exertion
- Swelling and oedema especially in lower body
- Fatigue
- Dizziness and fainting
- Chest pain
- Palpitations
- Cyanosis (lips and fingers turning blue)
- Hoarseness

We can determine the severity of PAH and at which stage is the patient through these symptoms (Figure 2)[7].

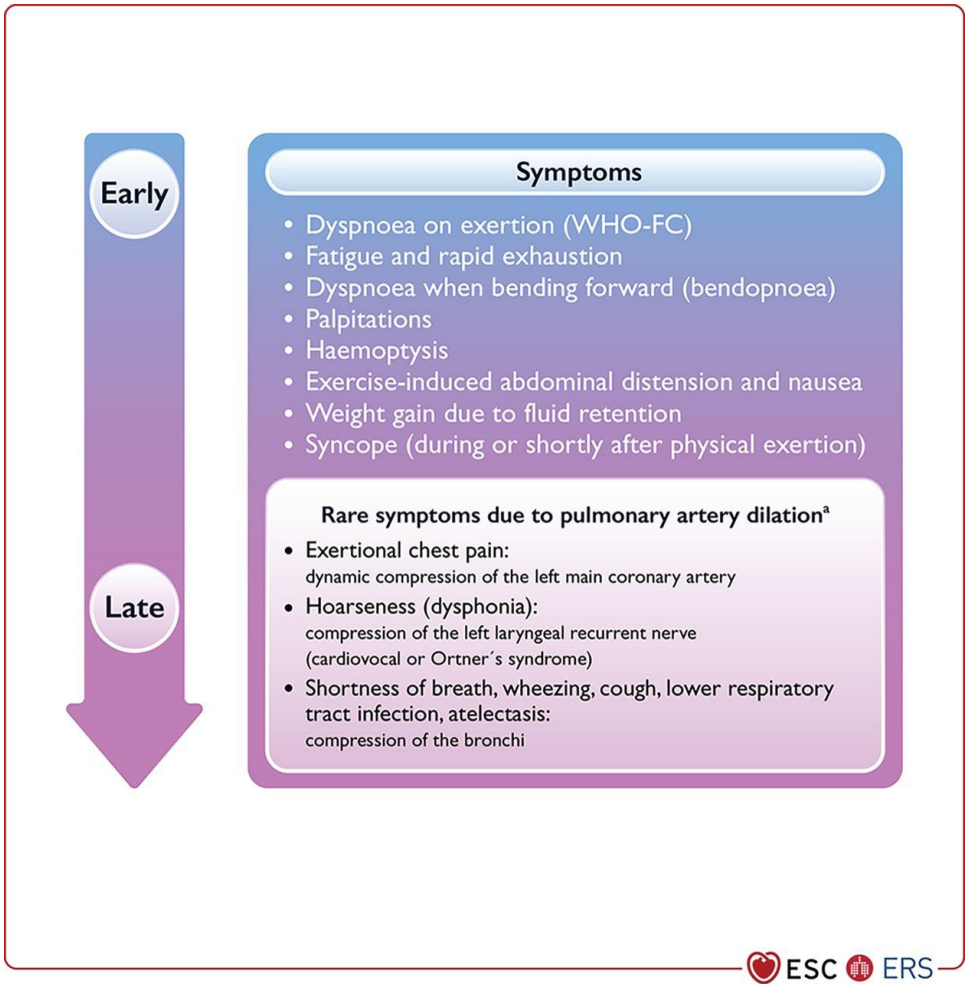



*Figure 2 Classification of severity of PAH symptoms* [9]

## 2.3 Diagnosis:

The detection of PAH or PH in general is still difficult despite the advancement in medical technology and equipment, it takes around 2 years to spot after the onset of the first symptoms[16]. It is recommended that anyone with symptoms of PH undergo a thorough medical examination and medical history checkup, combined with physical examination and blood pressure and heart rate monitoring, also oxygen monitoring and BNP (brain natriuretic peptide), and its precursor N-terminal BNP tests, and resting ECG, CPET (cardiopulmonary exercise tests) , cardiac and pulmonary function (PET), with the help of X-ray, echography and tomography [16] [9].

These screenings should be done to any patients presenting high risk factors including systemic sclerosis (since the prevalence of PAH is 5-19% in this group of people), and first-degree PAH relatives, BMPR2 mutation or liver transplantation. These screenings are recommended even if asymptomatic [9].

### 2.3.1 Algorithm of diagnosis:

1- Suspicion of PAH: the patient presents an unexplained dyspnoea or shortness of breath upon exercise, that prompts the doctor to evaluate cardiac and respiratory functions with: physical exercise, medical and family history, blood tests for BNP/NT-proBNP, and resting ECG[9].

2- Detection of PAH: using a non-invasive test to assess the cardiac function such as echocardiography to assign a probability of the existence of PAH, like an enlarged right atrial/right ventricle and an increases systolic PAP, also a presence of congenital heart defects[9].

3- Confirmation of PAH: Referral to a PH Centre is essential for detailed work-up in cases of intermediate/high probability of PH (based on echocardiography or other findings) or risk factors for PAH (connective tissue diseases, HIV, family history) or having a history of pulmonary embolism (PE) or signs of unresolved PE. The diagnosis involves an invasive testing such as right Heart Catheterization to confirm PH and determine the specific type and differentiate between pre-capillary PH (PAH) and post-capillary PH (due to left heart disease)[9].

At any time of the diagnosis process, any detection of warning signs needs to be delt with immediately since the prognosis is not ideal with PH or PAH, these warning signs and symptoms include: rapidly evolving or severe symptoms (FC III/IV), signs of RV failure such as oedema, syncope, symptoms low cardiac output, arrhythmias, and compromised haemodynamics (hypotension, tachycardia)[9] [16].

### 2.3.2 Differentiating between PAH and other PH:

There are a set of characteristics that are unique to PAH that can help in diagnosing patients with this disease, in which we can mention the more important ones as detailed in the guidelines for PH in the European respiratory society [9]:

**Chest radiography:** an increased size of right atrial or right ventricle and branching of peripheral blood vessels.

**Spirometry and PFT tests:** normal or impaired respiratory function depending on the stage of PAH (functional classification).

**Echocardiography:** increased systolic pressure and increased size of RA/RV, with absence of anomalies in the left heart.

**Right heart catheterisation:** same haemodynamic values as precapillary PH, mPAP more than 20 mmHg, and an **PAWP inferior to 15** and PVR more than 2 WOOD units.

**Cardiopulmonary exercise testing:** it is a valuable tool in assessing the mechanism and physiopathology of PH, while PAH patients exhibit a distinct pattern, a low end-tidal partial pressure of CO2, high ventilatory equivalent for carbon dioxide, low oxygen pulse and low peak oxygen intake. In PH patients a normal peak of oxygen uptake usually excludes PAH diagnosis.

# 3 Physiopathology of Pulmonary arterial hypertension:

PAH can be induced by several underlying causes or be entirely idiopathic, but no matter the case, we notice the same histological features, an increase in arteriole contractility, remodelling and proliferation of endothelial cells (leading to the thickening of the intima) and smooth muscles cells migration and proliferation leading to the muscularisation of distal arterioles, as well as a remodelling of the adventitia leading to fibrosis and infiltration of inflammatory cells and collagen disruption and plexiform lesions as a sign of severity [17], endothelial disfunction and hypercoagulation are to be noted as well [18]. These changes can be attributed to several signalling pathways:

## 3.1 Nitric Oxide pathway:

eNOS which is an enzyme in the endothelial cells of the vascular system, through the oxidation of an L-arginine to L-citrulline in the presence of NADPH and oxygen it produces NO, which then diffuses to the smooth muscle cells where it activates Guanylate cyclase enzyme, that then converts GTP (guanosine triphosphate) to GMP (guanosine monophosphate), this GMP in turns activates PKG, a protein kinase that phosphorylates myosin phosphatase leading to the unbinding of myosin chains (muscle relaxation) [19], also research showed that NO contribute to the inhibition of smooth muscle cell proliferation [20].

Although it would make sense that in a patient suffering from PAH they would have a lower level of eNOS expression, studies showed it is not the case, as they have shown elevated levels of eNOS in the plexiform lesions [21], making it more probable that the cause of the NO deficiency is due to the uncoupling of the enzyme by the unavailability of BH4 (tetrahydrobiopterin), or an elevated level of BH2 ( a product of BH4 oxidation by eNOS) since a coupling of the NOS is needed to generate NO instead of a superoxide (O2-), these BH2 molecules have been shown to have the same affinity for the binding site of BH4 on NOS, and it have been shown that elevated levels of BH2 can lead to the development of PAH in lamb as well [22].

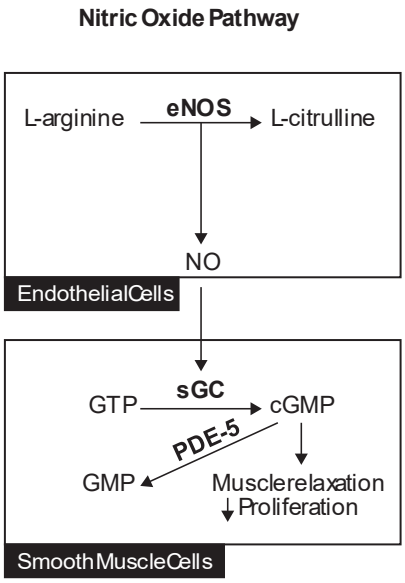



*Figure 3 Nitric oxide pathway*

## 3.2 Prostacyclin-Thromboxane A2 Pathway:

Prostacyclin is produced by the cleavage of an arachnoid acid usually from the membrane, by cyclooxygenase (1 or 2) giving us PGG2 then by the same enzyme a PGH2 that gets converted to either thromboxane A2 by thromboxane synthase or PGI2 by prostacyclin synthase, this PGI2 binds to a membrane G-coupled receptor (IP) leading to the activation of Adenylyl cyclase , that then increases the level of cAMP from ATP leading to the activation of PKA that causes muscle relaxation by the same mechanism of PKG, prostacyclin is also responsible for the inhibition of platelets aggregation and smooth muscle proliferation and also provides anti-inflammatory effects[18] .

In PAH patients there is a reduction in production of PGI2 and as well as a reduced IP receptors and prostacyclin synthase, leading to the dominance of the TXA2 pathway , thus leading overall to a reduction in vasodilatation and an increase in platelet aggregation[18].

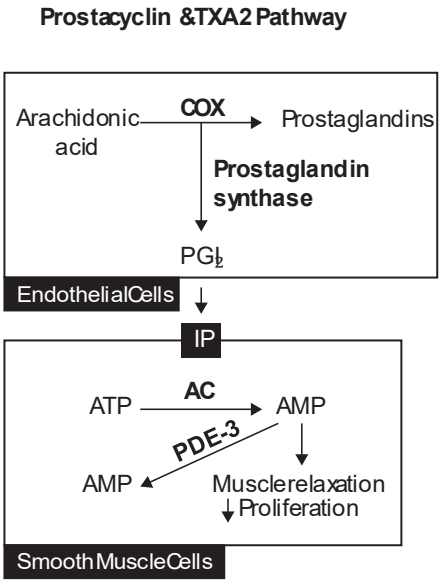



*Figure 4 Prostacyclin pathway*

## 3.3 Endothelin-1 Pathway :

Endothelin-1 is a peptide produced in the endothelial cells, that activates G-coupled receptors ETa on the smooth muscle cell level, and ETb receptors in smooth muscle cells and endothelial cells[18]. ETa is responsible for vasoconstriction, and ETb on the muscular level is a vasoconstrictor and on the endothelial cells level is an activator of NO and PGI2 production causing a vasodilatation[18].

PAH patients have usually an increase of ETa expression and downregulation of ETb as well as an elevated level of ET-1 causing an overall vasoconstriction[18].

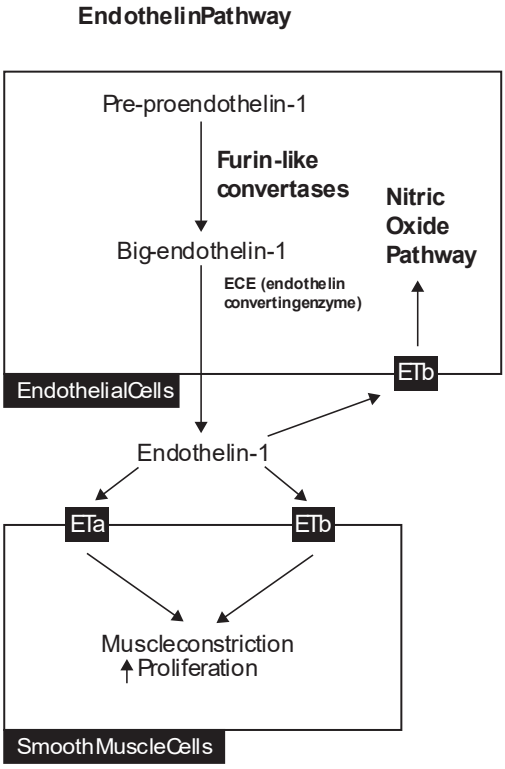



*Figure 5 Endothelin pathway*

## 3.4 Calcium channels in PAH:

An increase in cytosolic calcium levels (Ca2+) is a pivotal factor in the contractile, hyperproliferative, and anti-apoptotic behaviour of pulmonary arterial smooth muscle cells (PASMCs) in PAH. The regulation of calcium homeostasis is dependent upon ion channels that control the influx and sequestration of calcium within the sarcoplasmic reticulum and mitochondria[23].

In PAH, elevated cytosolic calcium levels have been linked to the overactivation of store-operated calcium channels, such as the transient receptor potential channel TrpC6, and a reduction in the expression of voltage-gated potassium channels, including Kv1.5. The downregulation of Kv1.5 results in a depolarisation of PASMC membranes, which in turn triggers an influx of calcium through voltage-dependent calcium channels. Restoration of Kv1.5 expression in rodent models through gene therapy has been demonstrated to result in improved haemodynamics. Prolonged elevations in cytosolic calcium levels drive cellular proliferation by stimulating the transition of cells into the cell cycle and the activation of NFAT, a transcription factor that is sensitive to calcium levels. Furthermore, NFAT suppresses

Kv1.5 expression, thus causing calcium overload, and increases the expression of bcl-2, which promotes resistance to apoptosis[23].

Also, mitochondrial calcium uptake is impaired due to reduced mitochondrial calcium uniporter (MCU) expression, which exacerbates cytosolic calcium levels. Rho kinase activation in PAH heightens calcium sensitivity, leading to excessive vasoconstriction and vascular stiffening, which is resistant to conventional vasodilators and inhibitors of Rho kinase, such as Fasudil, have demonstrated efficacy in small PAH studies, improving vasodilation and potentially reducing mortality in patients with right ventricular failure[23].

## 3.5 Role of the Transforming Growth Factor-Beta (TGF-β) Superfamily in PAH :

The transforming growth factor-beta (TGF-β) superfamily encompasses a large group of structurally related cytokines that regulate diverse cellular functions including proliferation, differentiation, migration, and survival. This superfamily includes TGF-βs, bone morphogenetic proteins (BMPs), growth differentiation factors (GDFs), activins, inhibins, and other related proteins[24] . Dysregulation of TGF-β superfamily signaling has emerged as a central pathogenic mechanism in PAH, particularly following the discovery of mutations in the BMPR2 gene in hereditary and idiopathic PAH cases[25]. TGF-β superfamily members signal through a pathway involving two types of serine/threonine kinase receptors (type I and type II) and intracellular Smad proteins, after ligand binding, type II receptors phosphorylate type I receptors, which then phosphorylate receptor-regulated Smads (R-Smads), these phosphorylated R-Smads form complexes with common-mediator Smad (co-Smad, Smad4), this complex is then transported to the nucleus where it regulates target gene expression [24] .

In the context of PAH, there are two primary branches of TGF-β superfamily signaling with opposing effects:

**BMP Signaling:** BMP ligands (particularly BMP2, BMP4, BMP9, and BMP10) bind to BMPR2 and BMP type I receptors (ALK1, ALK2, ALK3), activating Smad1/5/8 signaling, which generally promotes endothelial homeostasis, inhibits smooth muscle cell proliferation, and maintains vascular integrity [26].

**TGF-β/Activin Signaling:** TGF-β, activins, and GDFs bind to their respective type II receptors and type I receptors (primarily ALK4, ALK5, ALK7), activating Smad2/3 signaling, which in turn promotes cell proliferation, migration, and extracellular matrix production [24].

In healthy pulmonary vasculature, a balance between these signaling branches maintains vascular homeostasis. In PAH, however, this balance is disrupted, with reduced BMP/Smad1/5/8 signaling and enhanced TGF-β/activin/Smad2/3 signaling [24]. This imbalance promotes endothelial dysfunction, smooth muscle cell proliferation, and vascular remodeling, key features of PAH pathobiology .

Several mechanisms contribute to this signaling imbalance in PAH:

**BMPR2 Mutations:** Loss of function mutations in BMPR2 reduce BMP signaling capacity, shifting the balance toward TGF-β/activin signaling [27].

**Reduced BMPR2 Expression:** Even in the absence of mutations, BMPR2 expression is frequently downregulated in PAH due to inflammatory mediators, hypoxia, or epigenetic mechanisms [27].

**Increased TGF-β/Activin Ligands:** Enhanced production of TGF-β, activins, and GDFs further promotes the pro-proliferative Smad2/3 pathway [24].

**Dysregulation of BMP Co-receptors**: Alterations in co-receptors such as endoglin or BMP-binding proteins can affect BMP signaling efficiency [26].

**Crosstalk with Other Pathways:** Interactions with inflammatory, metabolic, and growth factor pathways further modulate TGF-β superfamily signaling .

Understanding the central role of TGF-β superfamily signaling in PAH pathogenesis has led to the development of therapeutic strategies aimed at restoring the balance between these signaling branches [24]. Sotatercept represents a pioneering approach in this direction, acting as a ligand trap for activins and GDFs to reduce pro-proliferative Smad2/3 signaling and indirectly enhance the anti-proliferative BMP/Smad1/5/8 pathway [28].

## 3.6 Bone Morphogenetic Protein (BMP) Signaling Pathway: Role in PAH Pathogenesis

The bone morphogenetic protein (BMP) signaling pathway, a key branch of the TGF-β superfamily, has emerged as a critical regulator of pulmonary vascular homeostasis and a central player in PAH pathogenesis [26].

The BMP signaling cascade begins with ligand binding to a heterotetrameric receptor complex consisting of two type II receptors (primarily BMPR2 in the pulmonary vasculature) and two type I receptors (ALK1, ALK2, or ALK3)[29].

In the pulmonary vascular system, BMP signaling through BMPR2 have an overall protective effect by [29]:

- Promoting endothelial cell survival and function
- Inhibiting smooth muscle cell proliferation and migration Preventing endothelial-to-mesenchymal transition
- Maintaining barrier function and vascular integrity Counterbalancing pro-proliferative TGF-β/activin signaling
- Regulating inflammatory responses

Disruption of BMP signaling is a central feature of PAH pathogenesis.

BMPR2 mutations are found in approximately 70-80% of heritable PAH cases and 20% of idiopathic PAH cases [26].

Notably, reduced BMPR2 expression and signaling are observed even in PAH patients without BMPR2 mutations, suggesting that this pathway represents a common pathogenic mechanism across various forms of PAH[26].

Several mechanisms contribute to dysregulated BMP signaling in PAH such as [26]:

- **BMPR2 Mutations**
- **Reduced BMPR2 Expression**.
- **Mutations in Other BMP Pathway Components:** Mutations in ALK1, Smad8, Smad1, BMP9, and other components of the BMP pathway have been identified in PAH patients .

- **Increased BMP Antagonists:** Elevated levels of BMP antagonists such as gremlin, noggin, and follistatin further inhibit BMP signaling .
- **Altered Expression of BMP Receptors and Co-receptors:** Changes in the expression or function of type I receptors and co-receptors like endoglin can modify BMP signaling efficiency.

Impaired BMP signaling leads to a series of molecular and cellular changes that promote PAH development [24,26]:

- Enhanced TGF-β/activin signaling through Smad2/3, promoting cell proliferation and extracellular matrix production.
- Increased endothelial cell apoptosis and dysfunction.
- Excessive smooth muscle cell proliferation and migration.
- Reduced nitric oxide production and vasodilation
- Enhanced inflammatory responses and immune cell recruitment Metabolic reprogramming toward a glycolytic phenotype

The central role of disrupted BMP signaling in PAH pathogenesis provides a strong rationale for therapeutic strategies aimed at restoring or enhancing this pathway. Approaches include directly augmenting BMP signaling (BMP ligand delivery, enhancing BMPR2 expression), inhibiting TGF β/activin signaling (TGF-β receptor inhibitors, ligand traps), or targeting downstream effectors or parallel pathways that interact with BMP signaling . Sotatercept represents an innovative approach in this category, acting as a ligand trap for activins and GDFs to rebalance the signaling between the BMP and TGF-β/activin pathways, thereby potentially addressing a fundamental pathobiological mechanism of PAH [28]

# 4 Current treatment and management of PAH:

In managing pulmonary hypertension (PH), an individualized, multi-faceted approach is essential following comprehensive diagnostic evaluations. Once any associated conditions are addressed and hemodynamic are clarified, treatment for pulmonary arterial hypertension (PAH) is designed based on evidence-based drug therapy, tailored according to patient profiles and PAH subtypes, as demonstrated in the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines[30].

Initial measures focus on supportive care, lifestyle modifications such as physical exercise and diet limiting sodium intake as well as psychological support, and appropriate referrals to specialized centers. Drug therapies are stratified by prognostic risk and the evidence strength for specific drugs, which may be used as monotherapy or in combination therapy. The treatment selection and combination approach are based on factors such as individual risk profiles, drug availability, and patient tolerance[30].

The drug treatment of PAH is based on targeting one or multiple of the previously mentioned pathways [31], and it has been shown the predominance of vascularly resistance mediated by the influx of calcium through the long lasting channels, which justifies the use of calcium channel blockers[31].

Current treatments are available in oral, parenteral and inhaled forms. These therapies are important in improving the quality of life of PAH patients, but they remain a symptomatic and disease slowing solution.

## 4.1 Calcium channel blockers:

These family of drugs including nifedipine, diltiazem and amlodipine are indicated for patients with positive acute vasoreactivity testing, noting that diltiazem is reserved for patients with tachycardia or other heart rate related problems, while it is avoided for bradycardia or a sign of right heart failure[31].

Usually patients are started on low doses than slowly increases to reach higher doses than other pathologies ( diltiazem from 240 mg to 720 mg daily [32]), with has some noticeable side effects ranging from lower body oedema and hypotension and digestive issues.

It is also to be noted that only less than 10% of patients are responders of calcium blockers for PAH, with an improvement of 5-year survival rate by 97% [31], so it is really important to assess the therapy on a patient to patient bases.

## 4.2 Phosphodiesterase Type-5 Inhibitors

The nitric oxide (NO) pathway plays a crucial role in maintaining pulmonary vascular homeostasis. NO, produced by endothelial cells, diffuses to adjacent smooth muscle cells, where it activates soluble guanylate cyclase (sGC) to convert guanosine triphosphate (GTP)

to cyclic guanosine monophosphate (cGMP). Elevated cGMP levels activate protein kinase G, leading to reduced intracellular calcium and subsequent vasodilation .

In PAH, NO synthesis and signaling are impaired, contributing to vasoconstriction and vascular remodeling [33]. Phosphodiesterase type-5 (PDE5) is the predominant phosphodiesterase isoform in the pulmonary vasculature and is responsible for degrading cGMP. PDE5 inhibitors prevent cGMP degradation, thereby enhancing and prolonging NO-mediated vasodilation , two PDE5 inhibitors are approved for PAH treatment [34]:

**Sildenafil:** Approved for WHO functional class II–III PAH, administered orally three times daily [35].

**Tadalafil:** Approved for WHO functional class IV PAH, administered once daily due to its longer half life[35]. Clinical trials have demonstrated that PDE5 inhibitors improve exercise capacity, WHO functional class, hemodynamics, and time to clinical worsening in PAH patients[36]. Common side effects include headache, flushing, dyspepsia, myalgia, and visual disturbances. PDE5 inhibitors are contraindicated with nitrates due to the risk of severe hypotension[37].

## 4.3 Soluble Guanylate Cyclase Stimulators :

Soluble guanylate cyclase (sGC) stimulators represent a newer class of drugs that target the NO pathway. Unlike PDE5 inhibitors, which prevent the degradation of cGMP, sGC stimulators directly stimulate sGC, increasing the production of cGMP even in the absence of endogenous NO [38]. This mechanism is particularly relevant in PAH, where NO bioavailability is often reduced . Riociguat is the only approved sGC stimulator for PAH[38]. It has a dual mode of action: it sensitizes sGC to endogenous NO and directly stimulates sGC independently of NO[39]. Riociguat is approved for the treatment of WHO functional class II-III PAH and chronic thromboembolic pulmonary hypertension (CTEPH) [40]. The PATENT-1 trial demonstrated that riociguat significantly improved exercise capacity, WHO functional class, pulmonary vascular resistance, and time to clinical worsening in PAH patients[41] . Common side effects include headache, dizziness, dyspepsia, peripheral edema, and hypotension. Riociguat is contraindicated with PDE5 inhibitors due to the risk of severe hypotension, and in pregnancy due to potential teratogenicity [41].

## 4.4 Prostacyclin Pathway Agents :

Prostacyclin (prostaglandin I2, PGI2) is primarily produced by endothelial cells and exerts potent vasodilatory, antiproliferative, and antithrombotic effects. In PAH, prostacyclin synthesis is reduced due to decreased expression of prostacyclin synthase in the pulmonary arteries, contributing to the pathogenesis of the disease . Prostacyclin and its analogs bind to the prostacyclin (IP) receptor, activating adenylate cyclase and increasing cyclic adenosine monophosphate (cAMP) levels, which leads to smooth muscle relaxation and inhibition of cell proliferation .

Several prostacyclin pathway agents are approved for PAH treatment:

**Epoprostenol:** A synthetic prostacyclin with a very short half-life (3-5 minutes), requiring continuous intravenous administration via an infusion pump. It is approved for WHO functional class III-IV PAH and is the only treatment shown to improve survival in advanced PAH in a randomized controlled trial [42] .

**Treprostinil:** A prostacyclin analog with a longer half-life (4 hours), available in intravenous, subcutaneous, inhaled, and oral formulations. It is approved for WHO functional class II-IV PAH, with the route of administration often determined by disease severity [43].

**Iloprost:** A prostacyclin analog administered via inhalation 6-9 times daily, approved for WHO functional class III-IV PAH [44]

**Selexipag:** An oral selective IP receptor agonist with a different chemical structure from prostacyclin but targeting the same receptor pathway. It is approved for WHO functional class II-III PAH [45].

Clinical trials have demonstrated that prostacyclin pathway agents improve exercise capacity, functional class, hemodynamics, and in some cases, clinical outcomes [46]. The GRIPHON trial showed that selexipag significantly reduced the risk of the primary composite endpoint of morbidity and mortality in PAH patients [47]. Common side effects of prostacyclin pathway agents include headache, flushing, jaw pain, diarrhea, nausea, musculoskeletal pain, and with parenteral forms, complications related to the delivery system (infection, pump malfunction) [46]. Abrupt discontinuation of these medications can lead to rebound pulmonary hypertension with clinical deterioration[46].

### 4.5 Endothelin Receptor Antagonists (ERAs):

Endothelin-1 is a 21-amino acid peptide produced primarily by vascular endothelial cells. In PAH, plasma ET-1 levels are significantly elevated due to increased production in endothelial cells and decreased pulmonary clearance. ET-1 exerts its biological effects through two G-protein-coupled receptor subtypes: ETA and ETB receptors [18,48].

ETA receptors are expressed predominantly on pulmonary smooth muscle cells and mediate potent vasoconstriction and cellular proliferation. ETB receptors are expressed predominantly on the endothelial surface of vessels and mediate vasodilation through nitric oxide and prostacyclin production; they also stimulate pulmonary clearance of circulating ET-1 to promote its elimination[48]. However, ETB receptors are also present in vascular wall muscle cells, where they have the same effects as ETA receptors (vasoconstriction and cellular proliferation).

In systemic and pulmonary hypertension, ETB receptor expression is upregulated in the media of blood vessels, and both ETA and ETB receptors contribute to the detrimental effects of ET-1.

**Bosentan:** Bosentan (Tracleer®) is a non-peptide pyrimidine derivative that was the first ERA approved for PAH treatment in 2001. It is a dual ETA and ETB receptor antagonist with an ETA:ETB selectivity ratio of 20:1 [51]

**Ambrisentan: The Selective ETA Antagonist**

Ambrisentan (Volibris®/Letairis®) is a propanoic acid derivative approved in 2007 as a selective ETA receptor antagonist with an exceptionally high ETA:ETB selectivity ratio of 200:1 [51]

**Macitentan: The Next-Generation ERA**

Macitentan (Opsumit®) is a next-generation dual ETA/ETB antagonist approved in 2013, developed by structural modification of bosentan to improve efficacy and safety. It has an ETA:ETB selectivity ratio of 50:1 [51]

## 4.6 Combination Therapy Approaches :

Given the complex pathophysiology of PAH involving multiple signaling pathways, combination therapy targeting different pathogenic mechanisms has become the standard of care for many PAH patients . Combination therapy can be initiated sequentially (adding a second or third drug when treatment goals are not met with monotherapy) or upfront (starting with two or more drugs simultaneously)[52]. The rationale for combination therapy includes [52]:

- Targeting multiple pathogenic pathways simultaneously
- Achieving additive or synergistic hemodynamic and clinical effects
- Allowing lower doses of individual drugs, potentially reducing side effects
- Addressing treatment tolerance issues by using complementary mechanisms

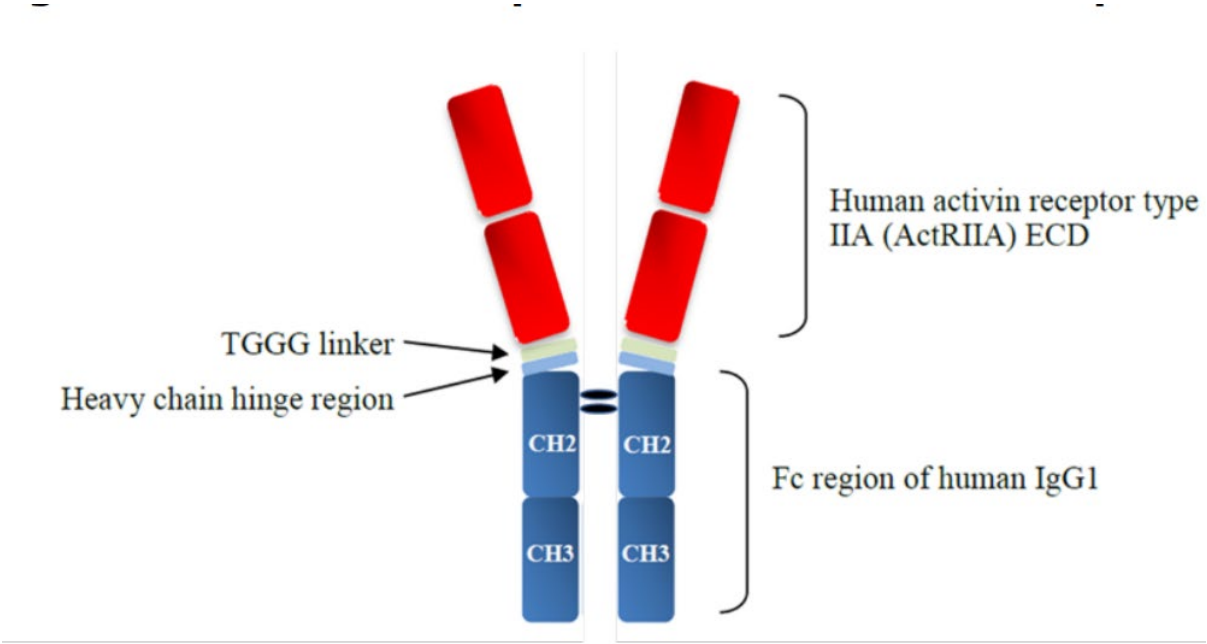
Several trials have demonstrated the benefits of combination therapy in PAH: The AMBITION trial[53] showed that initial combination therapy with ambrisentan and tadalafil was superior to monotherapy with either drug alone in reducing the risk of clinical failure events . The SERAPHIN trial[54] demonstrated that adding macitentan to background therapy (PDE5 inhibitor or prostanoid) reduced morbidity and mortality compared to placebo . The GRIPHON trial [47] showed that selexipag, when added to an ERA, PDE5 inhibitor, or both, reduced the risk of the primary composite endpoint of morbidity and mortality . Current guidelines recommend risk assessment-guided therapy, with low-risk patients potentially managed with monotherapy, while intermediate and high-risk patients often require double or triple combination therapy [34]. The most commonly used combinations include an ERA with a PDE5 inhibitor, with the addition of a prostacyclin pathway agent for more severe disease or inadequate response to dual therapy[34] .

# 5 Sotatercept (Winrevair) : Mechanism of Action :

## 5.1 Sotatercept as an Activin Receptor Ligand Trap :

Sotatercept (ACE-011) is a first-in-class fusion protein consisting of the extracellular domain of the activin receptor type IIA (ActRIIA) linked to the Fc portion of human immunoglobulin G1 (IgG1). This innovative structure enables sotatercept to function as a ligand trap for various members of the TGF-β superfamily, particularly activins, growth differentiation factors (GDFs), and to a lesser extent, some BMPs[55].

The design of sotatercept leverages the natural binding properties of ActRIIA, which serves as a type II receptor for multiple TGF-β superfamily ligands. By incorporating only the extracellular domain, sotatercept can bind these ligands with high affinity but lacks the intracellular signaling domain, effectively sequestering the ligands and preventing their interaction with endogenous receptors[55].




Abbreviations: CH2(3)= heavy chain constant region domain 2(3); ECD= extracellular domain; Fc= fragment crystallizable; TGGG= threonine-glycine-glycine-glycine

*Figure 6 Structure of Sotatercept[56]*

The Fc portion of the fusion protein serves multiple purposes[57]:

- Extending the half-life of the molecule through the neonatal Fc receptor recycling pathway
- Improving stability and solubility

- Potentially enhancing tissue distribution

Sotatercept exhibits high binding affinity for several TGF-β superfamily ligands, with particular selectivity for activin A, activin B, GDF8 (myostatin), GDF11, and to a lesser extent, BMP9 and BMP10[58]. This binding profile is critical to understanding its therapeutic effects in PAH, as these ligands participate in the dysregulated signaling processes that contribute to pulmonary vascular remodeling.

Originally developed for treating disorders of bone metabolism and anemia associated with chronic kidney disease, sotatercept's potential in PAH was recognized following observations that ActRIIA ligands, particularly activins and GDFs, are upregulated in PAH and contribute to the imbalance between BMP and TGF-β/activin signaling pathways[57,58]. By sequestering these ligands, sotatercept offers a novel approach to rebalancing these dysregulated pathways, potentially addressing a fundamental pathobiological mechanism of PAH[28,55].

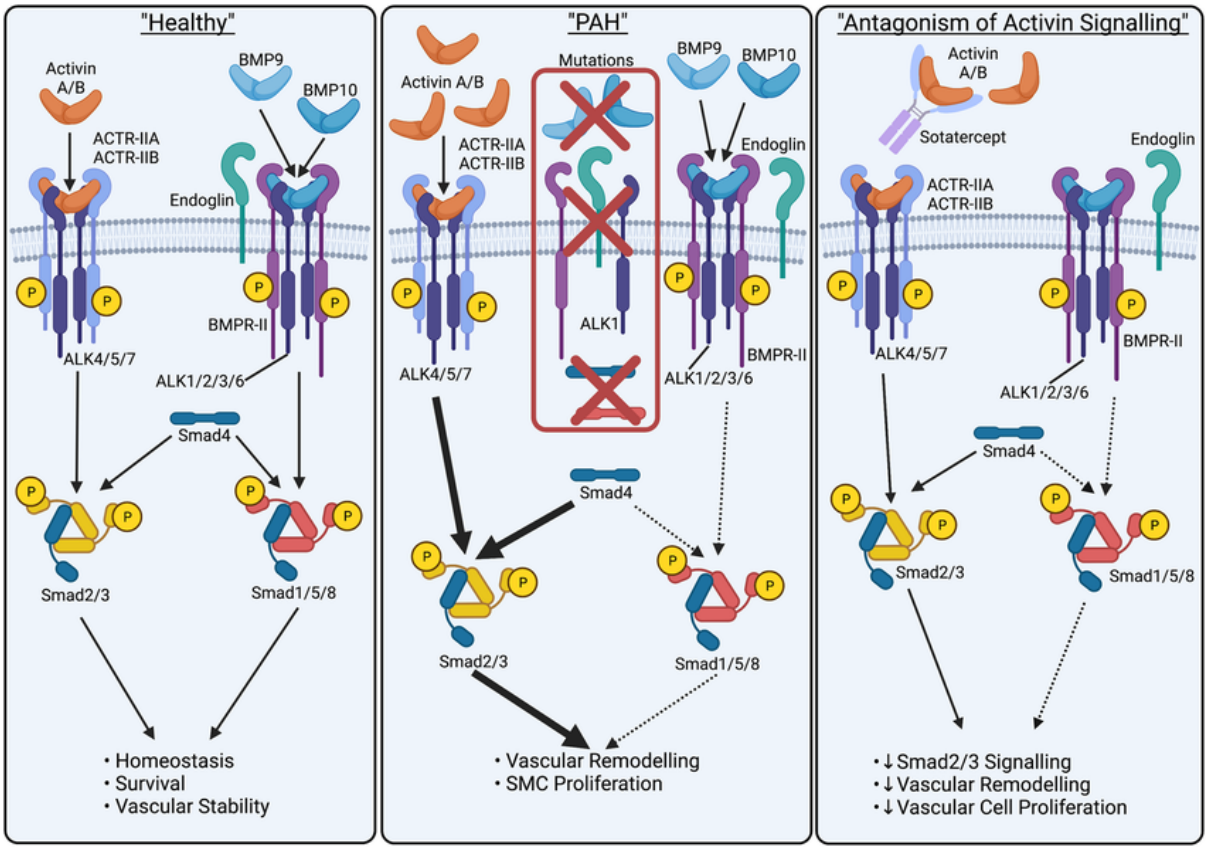



*Figure 7 A proposed mechanism of action of sotatercept[59]*

## 5.2 Impact on the TGF-β Superfamily Pathways

The therapeutic effect of sotatercept in PAH stems from its ability to rebalance the dysregulated TGF-β superfamily signaling pathways that are central to PAH pathogenesis

Sotatercept acts within this system by[55]:

1. **Direct Ligand Sequestration:** Sotatercept binds and neutralizes activins (particularly activin A and B) and GDFs (GDF8/myostatin and GDF11), preventing their interaction with endogenous receptors and reducing Smad2/3 signaling.
2. **Indirect Enhancement of BMP Signaling:** By reducing the competition for limited Smad4 (a common mediator for both signaling branches), sotatercept indirectly enhances BMP/Smad1/5/8 signaling.
3. **Reduction of BMP Antagonists:** Activin/GDF signaling can upregulate BMP antagonists like gremlin; by inhibiting this signaling, sotatercept may reduce BMP antagonist expression, further enhancing BMP pathway activity.
4. **Modulation of Receptor Expression:** Chronic activin/GDF signaling can downregulate BMPR2 expression; by inhibiting this signaling, sotatercept may help restore BMPR2 levels.
5. **Interference with ALK5-BMPR2 Heterodimerization:** Excessive activin/GDF signaling can promote heterodimerization between ALK5 and BMPR2, reducing canonical BMP signaling; sotatercept may prevent this interaction.

Through these mechanisms, sotatercept shifts the balance from the pro-proliferative, pro-fibrotic Smad2/3 pathway toward the anti-proliferative, homeostatic Smad1/5/8 pathway, potentially reversing the vascular remodeling processes that characterize PAH. This represents a fundamentally different approach compared to conventional PAH therapies, which primarily target vasoconstriction rather than the underlying vascular remodeling[55].

## 5.3 Restoration of BMPR2 Signaling in PAH :

The bone morphogenetic protein receptor type 2 (BMPR2) signaling pathway plays a crucial role in maintaining pulmonary vascular homeostasis, and its disruption is a central feature in

PAH pathogenesis. Sotatercept's ability to restore or enhance BMPR2 signaling represents a key aspect of its therapeutic potential in PAH.

It restores BMPR2 signaling by [55,58,60]:

1. **Relieving Competition for Smad4:** By reducing activin/GDF-mediated Smad2/3 phosphorylation, sotatercept decreases the competition for Smad4, allowing more Smad4 to participate in BMP/Smad1/5/8 signaling.
2. **Enhancing BMPR2 Expression:** Preclinical studies have shown that inhibition of activin/GDF signaling can restore BMPR2 expression levels, potentially by modulating transcriptional and post-transcriptional regulators of BMPR2[60].
3. **Reducing BMP Antagonists:** Activin/GDF signaling can upregulate BMP antagonists like gremlin; by inhibiting this signaling, sotatercept may reduce BMP antagonist expression, enhancing BMP ligand availability[60].
4. **Preventing Receptor Interference:** Excessive activin/GDF signaling can promote non-canonical interactions between ALK5 and BMPR2, impairing canonical BMP signaling; sotatercept may prevent these detrimental interactions.
5. **Modulating Co-receptor Expression:** By altering the signaling environment, sotatercept may influence the expression or function of BMP co-receptors that enhance BMPR2 signaling efficiency.

Importantly, even partial restoration of BMPR2 signaling may be sufficient to prevent or reverse PAH. Studies have shown that BMPR2 mutations have incomplete penetrance (approximately 20-30%)[61], suggesting that compensatory mechanisms or additional genetic/environmental factors influence disease development. By enhancing the remaining BMPR2 signaling capacity, sotatercept may help overcome the threshold required to maintain vascular homeostasis.

Preclinical studies have demonstrated that sotatercept treatment increases Smad1/5/8 phosphorylation and downstream gene expression in animal models of PAH, even without directly affecting BMPR2 expression levels. This suggests that the rebalancing of TGF-β superfamily signaling may be sufficient to restore adequate BMP pathway activity, even in the context of reduced BMPR2 expression or function[60,61].

## 5.4 Sotatercept's Effects on Vascular Remodeling and Inflammation in PAH :

Vascular remodeling represents a hallmark feature of PAH, characterized by endothelial dysfunction, excessive proliferation and apoptosis resistance of pulmonary arterial smooth muscle cells (PASMCs), fibrosis, inflammation, and in situ thrombosis[18,33]. Sotatercept's impact on these processes extends beyond its effects on TGF-β superfamily signaling, addressing multiple aspects of the complex pathobiology of PAH.

**Effects on Pulmonary Vascular Remodeling:**

1. **Endothelial Cell Function:** Sotatercept improves endothelial cell survival and function by restoring the balance between BMP and TGF-β/activin signaling. Enhanced BMP signaling promotes endothelial barrier integrity, reduces endothelial-to-mesenchymal transition, and improves angiogenic capacity[58].
2. **PASMC Proliferation and Apoptosis:** By inhibiting activin/GDF signaling and enhancing BMP signaling, sotatercept reduces PASMC proliferation and migration while promoting apoptosis of abnormal cells. This helps reverse the medial hypertrophy and muscularization of distal pulmonary arterioles characteristic of PAH[62].
3. **Fibrosis:** Activins and TGF-β are potent pro-fibrotic factors. By sequestering activins, sotatercept reduces fibroblast activation, differentiation into myofibroblasts, and excessive extracellular matrix production, potentially reversing adventitial and intimal fibrosis[63].
4. **Matrix Remodeling:** Sotatercept modulates the expression and activity of matrix metalloproteinases and their inhibitors, promoting a more balanced matrix turnover and reducing pathological vascular stiffness[64].
5. **Angiogenesis:** Restoration of balanced TGF-β superfamily signaling improves angiogenesis and may promote regeneration of lost pulmonary vasculature, particularly important in advanced PAH where vascular obliteration contributes to increased resistance[58].

**Effects on Inflammation in PAH:**

Inflammation plays a critical role in PAH pathogenesis, with perivascular infiltration of immune cells and elevated cytokine levels observed in patient samples and experimental models[167]. Sotatercept modulates inflammatory processes through several mechanisms:

1. **Reduction of Pro-inflammatory Cytokines:** Activins, particularly activin A, are potent inflammatory mediators. By sequestering activins, sotatercept reduces the production of pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α[65].
2. **Modulation of Immune Cell Function:** Sotatercept affects various immune cell populations, including macrophages, T cells, and B cells, potentially reducing their recruitment to the pulmonary vasculature and modulating their phenotypes toward less inflammatory states[66].
3. **Inhibition of NF-κB Signaling:** Activin signaling can promote NF-κB activation, a master regulator of inflammation. Sotatercept's inhibition of activin signaling may reduce NF-κB activity, decreasing inflammatory gene expression[63].
4. **Restoration of Endothelial Barrier Function:** By enhancing BMP signaling, sotatercept improves endothelial integrity, reducing vascular leakage and immune cell infiltration[55].
5. **Modulation of Oxidative Stress:** Sotatercept may reduce oxidative stress, a key driver of inflammation in PAH, through effects on mitochondrial function and antioxidant enzyme expression[65].

**Integrated Effects on PAH Pathophysiology:**

Preclinical studies have demonstrated that sotatercept treatment in animal models of PAH results in several beneficial effects that reflect its integrated impact on vascular remodeling and inflammation[60]:

1. Reduction in pulmonary arterial pressure and pulmonary vascular resistance
2. Decreased medial wall thickness and muscularization of distal pulmonary arteries
3. Reduced right ventricular hypertrophy and improved right ventricular function

4. Decreased perivascular inflammatory cell infiltration
5. Reduced expression of inflammatory and pro-fibrotic markers
6. Improved survival in severe PAH models

These effects collectively suggest that sotatercept has the potential to not only prevent further progression of PAH but also to reverse established disease, representing a significant advance over current therapies that primarily target vasoconstriction. The ability to address multiple aspects of PAH pathobiology through a single mechanism, rebalancing TGF-β superfamily signaling underlies sotatercept's promise as a transformative therapy for this devastating disease.

# 6 Comparative Analysis with Current PAH Treatments :

Sotatercept represents a paradigm shift in PAH treatment due to its unique mechanism of action, which fundamentally differs from currently approved therapies. Understanding these differences is essential for appreciating sotatercept's potential role in the therapeutic arsenal for PAH.

**Target Pathway Differences** [33,34,67]**:**

| **Drug Class** | **Primary Target Pathway** | **Mechanism of Action** | **Key Limitation** |
|---|---|---|---|
| Endothelin Receptor Antagonists | Endothelin Pathway | Block ET-1 binding to its receptors | Primarily affects vasoconstriction, limited effect on established vascular remodeling |
| PDE5 Inhibitors / sGC Stimulators | Nitric Oxide Pathway | Increase cGMP levels by preventing degradation or increasing production | Depends on intact NO synthesis; primarily vasodilatory effects |

| Drug Class | Primary Target Pathway | Mechanism of Action | Key Limitation |
|---|---|---|---|
| Prostacyclin Analogs / IP Receptor Agonists | Prostacyclin Pathway | Activate the IP receptor, increasing cAMP levels | Complex administration (for prostacyclins); primarily vasodilatory, though some anti-proliferative effects |
| Sotatercept | TGF-β/BMP Signaling Pathway | Rebalances TGF-β superfamily signaling by sequestering activins and GDFs | May have delayed onset of action compared to direct vasodilators |

While current therapies primarily target pathways involved in vasoconstriction (a symptom of PAH), sotatercept addresses a fundamental pathobiological mechanism directly linked to vascular remodeling (a cause of PAH). This distinction is crucial, as vascular remodeling is the primary driver of disease progression and morbidity in PAH[55,63].

**Disease-Modifying Potential vs. Symptomatic Treatment:**

Current PAH therapies are generally considered symptomatic treatments that slow disease progression but do not usually induce disease regression. In contrast, sotatercept has demonstrated potential disease-modifying effects[60,62]:

1. **Reversal of Vascular Remodeling:** Preclinical studies show that sotatercept can reverse established vascular lesions in animal models of PAH, suggesting potential for disease regression rather than merely slowing progression[60].

2. **Targeting Genetic Mechanisms:** By addressing the signaling imbalance resulting from BMPR2 mutations or downregulation, sotatercept targets a genetic/molecular root cause of PAH[55,60].

3. **Multiple Cellular Effects:** Sotatercept affects multiple cell types involved in PAH pathogenesis (endothelial cells, smooth muscle cells, fibroblasts, immune cells) through a single mechanism, potentially providing more comprehensive disease modification[55,60].

4. **Durable Response:** Clinical trial data suggest that the hemodynamic and functional improvements with sotatercept may be more durable than those observed with conventional vasodilators, consistent with structural rather than purely functional changes[62].

**Vasodilatory vs. Anti-Remodeling Effects:**

A key distinction between sotatercept and conventional PAH therapies lies in their primary effects on the pulmonary vasculature:

1. **Conventional Therapies:** Primarily induce vasodilation, with secondary or limited effects on vascular remodeling. Improvements in pulmonary vascular resistance (PVR) are often accompanied by increases in cardiac output, reflecting the functional vasodilatory effect[18].

2. **Sotatercept:** Primarily targets vascular remodeling, with improvements in PVR driven mainly by reductions in mean pulmonary arterial pressure rather than increases in cardiac output. This pattern suggests structural changes in the pulmonary vasculature rather than purely functional vasodilation[55].

**Practical Aspects and Clinical Implications:**

1. **Administration:** Sotatercept is administered subcutaneously every 3 weeks, offering a convenient dosing schedule compared to daily oral medications or continuous infusions required for some prostacyclin analogs[56].

2. **Side Effect Profile:** Sotatercept's side effects (primarily hematological effects like increased hemoglobin and thrombocytopenia) differ from those of conventional PAH

therapies, potentially offering an alternative for patients intolerant to current treatments[56].

3. **Combination Potential:** Sotatercept's distinct mechanism of action suggests potential for additive or synergistic effects when combined with conventional PAH therapies, which has been observed in clinical trials where most patients were on background combination therapy[68].

4. **Biomarkers:** Sotatercept's effects may be monitored through different biomarkers than conventional therapies, potentially including TGF-β superfamily ligands and signaling components, offering new opportunities for personalized therapy[66].

In summary, sotatercept represents a fundamentally different approach to PAH treatment compared to current therapies. While conventional treatments primarily address the symptom of vasoconstriction, sotatercept targets a root cause of PAH, dysregulated TGF-β/BMP signaling, with the potential to reverse vascular remodeling and modify the course of the disease. This novel approach may complement existing therapies and offer hope for improved long-term outcomes in this devastating disease.

# 7 Clinical Trials of Sotatercept in Pulmonary Arterial Hypertension :

The translation of sotatercept's promising preclinical findings into human clinical trials has yielded remarkable results, positioning this agent as a potential paradigm-shifting therapy for PAH. This section details the key clinical trials that have evaluated sotatercept's safety, tolerability, pharmacokinetics, and efficacy in PAH patients.

## 7.1 Phase I Clinical Trials: Safety, Tolerability, and Pharmacokinetics :

Initial clinical development of sotatercept focused on healthy volunteers and patients with anemia or bone disorders, providing important foundational data on safety and pharmacokinetics prior to PAH-specific studies[69].

Key findings from these Phase I studies included:

1. **Pharmacokinetics:** Sotatercept demonstrated dose-proportional exposure, with a half-life of approximately 23 days, supporting administration every 3 weeks[69].

2. **Safety:** Most adverse events were mild to moderate in severity, with hematological effects (increased hemoglobin, reduced platelets) being most common and consistent with the drug's mechanism of action[7].

3. **Dose-Response:** Clear dose-dependent effects on pharmacodynamic markers, particularly erythropoiesis, were observed, informing dose selection for subsequent PAH trials[70].

## 7.2 Phase II PULSAR Trial: Efficacy and Safety Outcomes :

The PULSAR trial (NCT03496207) was a pivotal, multicenter, randomized, double-blind, placebo-controlled Phase II study that evaluated the efficacy and safety of sotatercept in patients with PAH[7]. The trial enrolled 106 patients with WHO Group 1 PAH who were on stable background therapy for at least 90 days. Patients were randomized 1:1:1 to receive placebo, sotatercept 0.3 mg/kg, or sotatercept 0.7 mg/kg subcutaneously every 3 weeks for 24 weeks[7].

The primary endpoint was the change from baseline to week 24 in pulmonary vascular resistance (PVR). Key secondary endpoints included six-minute walk distance (6MWD), N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, WHO functional class, and time to clinical worsening[7].

The PULSAR trial demonstrated remarkable efficacy of sotatercept:

1. **Primary Endpoint:** Sotatercept significantly reduced PVR compared to placebo, with placebo-corrected reductions of -20.5% ($p=0.03$) in the 0.3 mg/kg group and -33.9% ($p<0.001$) in the 0.7 mg/kg group[7,71].

2. **6MWD:** Significant improvements in 6MWD were observed, with placebo-corrected increases of +29.4 meters ($p=0.03$)[72].

3. **NT-proBNP:** Sotatercept significantly reduced NT-proBNP levels, with geometric mean ratios (versus placebo) of 0.58 ($p=0.003$) for the 0.3 mg/kg dose and 0.48 ($p<0.001$) for the 0.7 mg/kg dose[70,72].

4. **WHO Functional Class:** A higher proportion of patients treated with sotatercept showed improvement in WHO functional class compared to placebo[72].

5. **Clinical Worsening:** Fewer patients experienced clinical worsening events in the sotatercept groups compared to placebo, although the trial was not powered for this endpoint[72].

Notably, the hemodynamic improvements with sotatercept were primarily driven by reductions in mean pulmonary arterial pressure rather than increases in cardiac output, consistent with structural remodeling of the pulmonary vasculature rather than acute vasodilation[72].

### 7.2.1 Improvement in Hemodynamics, Exercise Capacity, and Quality of Life :

Detailed analyses of the PULSAR trial and its open-label extension provided comprehensive insights into sotatercept's effects on various aspects of PAH:

**Hemodynamic Effects:**

1. **Mean Pulmonary Arterial Pressure (mPAP):** Sotatercept significantly reduced mPAP, with placebo-corrected reductions of -6.0 mmHg (p=0.002) in the 0.3 mg/kg group and -8.0 mmHg (p<0.001) in the 0.7 mg/kg group[71,72].
2. **Cardiac Index:** No significant changes in cardiac index were observed, suggesting that PVR reductions were not due to increased cardiac output[72].
3. **Right Atrial Pressure:** Sotatercept reduced right atrial pressure, reflecting improved right ventricular function[72].
4. **Mixed Venous Oxygen Saturation:** Improved mixed venous oxygen saturation was observed, indicating better tissue oxygen delivery[72].

**Exercise Capacity and Functional Status:**

1. **6MWD**.
2. **WHO Functional Class improvement**
3. **Borg Dyspnea Index:** Reduced dyspnea scores following the 6-minute walk test indicated improved exercise tolerance[72].

**Quality of Life and Patient-Reported Outcomes[28]:**

1. **PAH-SYMPACT Questionnaire:** Improvements in patient-reported symptoms and impacts were observed, particularly in physical impact and cardiopulmonary symptom domains.
2. **EQ-5D:** Better health-related quality of life scores were reported by sotatercept-treated patients.

## 7.3 PULSAR Open-Label Extension and SPECTRA Studies :

The open-label extension (OLE) of the PULSAR trial provided valuable data on the long-term efficacy and safety of sotatercept. Nearly all patients (97%) from the PULSAR trial enrolled in the OLE, receiving sotatercept at doses of 0.3 mg/kg or 0.7 mg/kg every 3 weeks, with option for dose adjustments based on tolerability and hemoglobin levels[73].

Key findings from the OLE, with data up to 48 weeks, included:

1. **Sustained Efficacy:** Improvements in PVR, 6MWD, and NT-proBNP were maintained or enhanced during extended treatment[73].
2. **Durable Response:** Patients originally randomized to placebo who switched to sotatercept showed improvements similar to those observed in the active treatment arms of the main trial[72].
3. **Long-term Safety:** No new safety signals emerged with extended treatment, and the frequency of adverse events decreased over time[73].

The SPECTRA study (NCT03738150) was a single-arm, open-label, exploratory Phase II trial that assessed the effects of sotatercept on cardiopulmonary exercise testing parameters in PAH patients[74]. This study provided complementary data on sotatercept's impact on exercise physiology, demonstrating improvements in peak oxygen consumption, ventilatory efficiency, and other exercise parameters.

## 7.4 Phase III STELLAR Trial :

The STELLAR trial (NCT04576688) was a pivotal, multicenter, randomized, double-blind, placebo-controlled Phase III trial that evaluated the efficacy and safety of sotatercept in patients with PAH[250]. This larger trial enrolled 323 patients with WHO Group 1 PAH who

were on stable background therapy. Patients were randomized 1:1 to receive sotatercept 0.7 mg/kg or placebo subcutaneously every 3 weeks for 24 weeks[75].

The primary endpoint was the change from baseline to week 24 in 6MWD. Secondary endpoints, tested hierarchically, included multicomponent improvement, PVR, NT-proBNP, WHO functional class, time to death or clinical worsening, French risk score, and changes in the PAH-SYMPACT physical, cardiopulmonary, and cognitive/emotional domains.

The STELLAR trial demonstrated robust efficacy across nearly all endpoints[75]:

1. **Primary Endpoint:** Sotatercept significantly improved 6MWD compared to placebo, with a placebo-corrected increase of +40.8 meters (95% CI: 27.5 to 54.1; $p<0.001$)[75].
2. **Secondary Endpoints:** Eight of nine secondary endpoints were met, including significant improvements in PVR, NT-proBNP, multicomponent improvement, WHO functional class, time to death or clinical worsening, and patient-reported outcomes[75].
3. **Consistency Across Subgroups:** Benefits were observed across various subgroups, including different background therapies, PAH etiologies, and baseline risk categories.

The magnitude of benefit observed in the STELLAR trial was considered clinically meaningful and potentially transformative, particularly given that most patients were already on optimal background therapy including combinations of approved PAH medications[75].

## 7.5 Adverse Effects and Safety Profile in Clinical Trials :

The safety profile of sotatercept in PAH clinical trials has been generally acceptable, with most adverse events being manageable and consistent with the drug's mechanism of action.

The most commonly reported adverse events associated with sotatercept included[72,75]:

1. **Hematological Effects:** Increased hemoglobin levels (dose-dependent) were common, occasionally requiring dose reduction or temporary interruption. Thrombocytopenia was also observed in some patients.
2. **Telangiectasia:** Development of telangiectasias (small dilated blood vessels near the skin surface) was reported, particularly with longer treatment duration.

3. **Epistaxis (Nosebleeds):** More frequent in sotatercept-treated patients, possibly related to vascular effects.
4. **Dizziness:** Reported more commonly with sotatercept than placebo.
5. **Blood Pressure Increases:** Small increases in systemic blood pressure were observed in some patients.
6. **Headache and Gastrointestinal Symptoms:** Headache, diarrhea, and other gastrointestinal symptoms were reported.

Serious adverse events were infrequent and generally not attributed to sotatercept. In the PULSAR and STELLAR trials, rates of discontinuation due to adverse events were low, indicating acceptable tolerability[72,75,76].

Risk mitigation strategies for managing sotatercept-related adverse events have been developed, including[76]:

1. Regular monitoring of hemoglobin levels, with dose adjustments or temporary interruptions for excessive increases
2. Platelet count monitoring
3. Blood pressure monitoring
4. Patient education regarding potential symptoms requiring medical attention

Importantly, the frequency of adverse events tended to decrease with longer exposure to sotatercept in the open-label extension studies, suggesting potential adaptation or management strategies that improve tolerability over time[76].

The overall risk-benefit profile of sotatercept has been considered favorable, particularly given the significant efficacy demonstrated across multiple endpoints and the serious, progressive nature of PAH, The safety profile supports sotatercept's potential role as a valuable addition to the therapeutic armamentarium for PAH, although continued vigilance and long-term safety monitoring will be important as clinical experience with the drug expands[68,76].

# 8 Sotatercept in Combination Therapy for PAH :

Combination therapy has become the standard of care for many patients with PAH, reflecting the complex pathobiology of the disease and the limited efficacy of monotherapy. Sotatercept's unique mechanism of action makes it particularly attractive as an add-on therapy to existing PAH medications, potentially providing complementary or synergistic effects through targeting different pathobiological pathways[73,76].

## 8.1 Current Standard of Care in PAH: Combination Therapies :

The evolution of PAH treatment strategies has shifted from sequential monotherapy to upfront combination therapy based on several landmark trials showing improved outcomes with combination approaches:

1. **AMBITION Trial:** Demonstrated superior outcomes with initial combination therapy (ambrisentan plus tadalafil) compared to either monotherapy in treatment-naïve PAH patients[77].
2. **SERAPHIN Trial:** Showed benefits of adding macitentan to background PAH therapy[78].
3. **GRIPHON Trial:** Demonstrated reduced morbidity/mortality with selexipag addition to background therapy[79].

Current guidelines recommend combination therapy approaches based on risk assessment:

1. **Low-Risk Patients:** May be managed with monotherapy or dual combination therapy[34]
2. **Intermediate-Risk Patients:** Initial dual oral combination therapy (typically an ERA plus PDE5i) is recommended[34]
3. **High-Risk Patients:** Initial triple combination therapy including a parenteral prostacyclin is often recommended[34]

Despite these advances, many patients on combination therapy continue to deteriorate or fail to achieve low-risk status, highlighting the need for novel therapeutic approaches like sotatercept[34,67].

## 8.2 Sotatercept as an Add-on to Existing PAH Therapies :

A key feature of the clinical development program for sotatercept is that the drug was evaluated primarily as an add-on to optimized background therapy rather than as monotherapy[62,73]. In the Phase II PULSAR trial and Phase III STELLAR trial, the vast majority of patients were receiving one or more approved PAH therapies at baseline:

1. **Background Therapy in PULSAR:** Approximately 56% of patients were on double combination therapy and 32% on triple combination therapy at enrollment[73].
2. **Background Therapy in STELLAR:** Over 75% of patients were on double or triple combination therapy, with most patients receiving an ERA plus a PDE5i, and approximately one-third also receiving a prostacyclin pathway agent[62].

This study design reflects the ethical considerations of conducting trials in a serious disease with established therapies, but also provides directly applicable evidence for sotatercept's use in the real-world setting, where most PAH patients are already receiving combination therapy.

Subgroup analyses from these trials have provided valuable insights into sotatercept's efficacy when added to specific background therapies:

1. **Dual Oral Background Therapy:** Patients on an ERA plus PDE5i showed significant improvements with sotatercept addition, with magnitudes of benefit similar to or greater than the overall trial populations[80].
2. **Triple Therapy (including Prostacyclin):** Even patients on triple therapy, who typically have more advanced disease, demonstrated meaningful benefits with sotatercept addition, suggesting value in this difficult-to-treat population[62].
3. **Consistency Across Regimens:** The benefits of sotatercept were generally consistent regardless of the specific background regimen, supporting its broad applicability across different treatment combinations[81].

## 8.3 Synergistic Effects in Reducing Pulmonary Vascular Resistance :

The mechanistic rationale for combining sotatercept with existing PAH therapies lies in their complementary effects on different pathobiological pathways:

1. **Vasodilation plus Anti-Remodeling:** While conventional PAH therapies primarily target vasoconstriction through the nitric oxide, prostacyclin, and endothelin pathways, sotatercept addresses the underlying vascular remodeling by rebalancing TGF-β/BMP signaling[55].
2. **Functional plus Structural Effects:** Conventional therapies produce mainly functional improvements in pulmonary vascular tone, while sotatercept potentially induces structural changes in the pulmonary vasculature[81].
3. **Distinct Cellular Targets:** The combination may affect different cell types and processes involved in PAH pathogenesis more comprehensively than either approach alone[80].

Analyses of hemodynamic data from clinical trials suggest potential synergistic effects when sotatercept is added to background therapy:

1. **PVR Reduction Mechanism:** While PDE5 inhibitors and prostacyclins typically reduce PVR primarily by increasing cardiac output, sotatercept reduces PVR mainly by decreasing mean pulmonary arterial pressure, suggesting complementary mechanisms[62].
2. **Magnitude of Benefit:** The substantial additional reductions in PVR when sotatercept was added to optimized background therapy (including combinations) suggest additive or potentially synergistic effects rather than merely independent actions[80].
3. **Durable Response:** The durability of hemodynamic improvements observed in the extension studies suggests that the combination may provide more sustained benefits than typically observed with vasodilator therapies alone[81].

## 8.4 Comparative Efficacy with Other Emerging Therapies :

Several other novel therapeutic approaches for PAH are in various stages of clinical development, each targeting different aspects of the disease pathobiology. Comparing sotatercept with these emerging therapies provides context for its potential role in the evolving treatment landscape:

| Emerging Therapy | Mechanism of Action | Development Stage | Comparative Considerations vs. Sotatercept |
|---|---|---|---|
| Inhaled Imatinib[82] | Tyrosine kinase inhibitor; anti-proliferative | Phase III | Different anti-remodeling mechanism; inhaled vs. subcutaneous; shorter half-life requiring daily administration |
| Seralutinib (GB002)[83] | Inhaled PDGF receptor inhibitor | Phase II | More selective tyrosine kinase inhibition; inhaled administration; targets different signaling pathway |
| Ralinepag[84] | Oral IP receptor agonist | Phase III | Primarily vasodilatory; targets prostacyclin pathway; potentially complementary to sotatercept |
| CXA-10[85] | Nitrated fatty acid; anti-inflammatory, anti-fibrotic | Phase II | Different anti-inflammatory/anti-fibrotic mechanism; oral administration |
| Elafin[86] | Elastase inhibitor; anti-inflammatory | Phase II | Focused on inflammatory component; different mechanism and target pathway |

While direct comparative trials are lacking, several aspects of sotatercept's clinical profile appear particularly distinctive:

1. **Magnitude of Efficacy:** The improvements in 6MWD, PVR, and other endpoints observed with sotatercept exceed those typically reported with most other investigational agents in Phase II/III development.

2. **Consistency Across Endpoints:** Sotatercept has demonstrated benefits across multiple domains (hemodynamics, exercise capacity, functional class, biomarkers, patient-reported outcomes), suggesting broader disease-modifying effects[80].
3. **Target Population:** Sotatercept has shown efficacy across a wide range of PAH subgroups and in patients already on optimal background therapy, positioning it potentially as a broadly applicable add-on therapy[80].
4. **Administration:** The subcutaneous route and extended dosing interval (every 3 weeks) offer practical advantages over some competitors requiring more frequent or complex administration[80].

Looking forward, the most effective approach to PAH management may involve combinations of these novel therapies with complementary mechanisms, potentially including sotatercept plus targeted anti-proliferative, anti-inflammatory, or metabolic agents. The distinct mechanism of sotatercept suggests potential for combination not only with conventional vasodilators but also with other emerging therapies targeting different aspects of PAH pathobiology

# 9 Long-term Benefits of Sotatercept in PAH Management :

While the short-term efficacy of sotatercept in PAH has been well-established in Phase II and III clinical trials, understanding its long-term benefits is crucial for determining its place in the treatment paradigm of this chronic, progressive disease. Emerging data from extension studies and ongoing research provide insights into sotatercept's potential for disease modification, impact on survival and disease progression, effects on quality of life, and economic considerations.

## 9.1.1 Potential for Disease Modification in PAH :

Disease modification in PAH refers to the ability of a therapy to alter the underlying pathobiology of the disease, rather than merely providing symptomatic relief. Several characteristics of sotatercept suggest potential for true disease modification:

1. **Targeting Fundamental Pathobiology:** By addressing the dysregulated TGF-β/BMP signaling that is central to PAH pathogenesis, particularly in patients with BMPR2 mutations, sotatercept targets a root cause of the disease rather than just its manifestations[55].
2. **Reversal of Vascular Remodeling**
3. **Hemodynamic Pattern of Response:** The reduction in pulmonary vascular resistance driven primarily by decreased mean pulmonary arterial pressure rather than increased cardiac output suggests effects on vascular structure rather than acute vasodilation[55].
4. **Durability of Response:** Data from extension studies show sustained or even increasing benefits over time, consistent with progressive structural remodeling rather than the plateauing often seen with vasodilator therapies[80].
5. **Biomarker Changes:** Improvements in markers of right ventricular stress (NT-proBNP) and potentially in markers of vascular remodeling suggest fundamental changes in disease processes[80].

While definitive evidence of disease modification would require demonstration of improved long-term outcomes or changes in the natural history of the disease, the available data provide encouraging indications that sotatercept may offer more than symptomatic improvement[80].

### 9.1.2 Impact on Disease Progression, Right Ventricular Function, and Survival :

Right ventricular function is the primary determinant of survival in PAH, and therapies that preserve or improve right ventricular adaptation to increased afterload are particularly valuable. Evidence regarding sotatercept's effects on key prognostic indicators includes:

**Right Ventricular Function:**

1. **NT-proBNP Reduction:** Significant and sustained reductions in NT-proBNP levels with sotatercept indicate decreased right ventricular wall stress[81].

2. **Echocardiographic Parameters:** Improvements in right ventricular function parameters, including tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change, have been observed[62].

3. **Right Atrial Pressure:** Reductions in right atrial pressure suggest improved right ventricular function and potentially reduced risk of right heart failure[74].

4. **Cardiac MRI Studies:** Preliminary cardiac MRI data suggest potential improvements in right ventricular structure and function with sotatercept treatment[316].

**Disease Progression:**

1. **Clinical Worsening Events:** Reduced risk of clinical worsening events (hospitalization, disease progression, PAH therapy escalation, death) has been observed with sotatercept compared to placebo[62].

2. **WHO Functional Class:** Improvements or maintenance of WHO functional class over extended periods suggest stabilization or reversal of disease progression[62].

3. **Exercise Capacity:** Sustained improvements in 6MWD during long-term treatment indicate durable functional benefits[62].

4. **Risk Assessment Scores:** Improvements in validated risk assessment tools (REVEAL, French risk assessment method) with sotatercept treatment suggest reduced mortality risk[87].

**Survival:**

While the clinical trials to date have not been designed or powered primarily to assess mortality, several observations are relevant to potential survival benefits:

1. **Mortality Signal:** Numerical reductions in mortality were observed in the sotatercept groups compared to placebo in the STELLAR trial, though the studies were not powered for this endpoint[68].

2. **Surrogate Endpoints:** Improvements in established prognostic indicators (PVR, 6MWD, NT-proBNP, functional class) that correlate with survival in PAH suggest potential for mortality benefit[88].

3. **Risk Category Shifts:** Movement of patients from higher to lower risk categories with sotatercept treatment is associated with improved predicted survival based on registry data[88].

Ongoing long-term studies and registries will provide more definitive data on sotatercept's impact on survival and disease progression. The SOTERIA study, an open-label extension of the STELLAR trial[62,76], is collecting long-term efficacy and safety data that will further inform understanding of sotatercept's effects on disease trajectory.

### 9.1.3 Health-Related Quality of Life and Patient-Centered Outcomes

Beyond physiological and functional improvements, sotatercept has demonstrated significant benefits in health-related quality of life and patient-reported outcomes, which are critically important aspects of therapy in a chronic, debilitating disease like PAH[62]:

1. **PAH-SYMPACT Questionnaire:** Significant improvements in multiple domains of this PAH-specific quality of life instrument have been observed with sotatercept, particularly in physical functioning and cardiopulmonary symptoms.
2. **Dyspnea Scores:** Reduced Borg dyspnea scores following exercise testing indicate improved symptomatic burden.
3. **Functional Independence:** Improvements in physical functioning may translate to greater independence in activities of daily living and reduced caregiver burden.
4. **Treatment Burden:** The subcutaneous administration every 3 weeks represents a relatively low treatment burden compared to daily oral medications or continuous infusions required for some PAH therapies.
5. **Psychological Well-being:** Improvements in disease symptoms and functioning may contribute to better psychological outcomes, including reduced anxiety and depression, which are common in PAH.

These patient-centered benefits are particularly important considering that PAH significantly impairs quality of life through physical limitations, emotional distress, social isolation, and reduced ability to fulfill family and occupational roles. Therapies that improve both quantity and quality of life represent the ideal goal of PAH management.

### 9.1.4 Cost-Effectiveness in Clinical Practice

As with many innovative therapies for rare diseases, considerations of cost, cost-effectiveness, and patient access are important aspects of sotatercept's integration into clinical practice:

**Economic Considerations:**

1. **Direct Treatment Costs:** While specific pricing information is still evolving, biologic therapies like sotatercept typically have substantial acquisition costs[89].
2. **Offset Costs:** Potential reductions in hospitalization, disease progression, and need for additional therapies may partially offset direct treatment costs[90].
3. **Quality-Adjusted Life Years (QALYs):** Improvements in survival and quality of life with sotatercept may translate to QALY gains that support cost-effectiveness despite high acquisition costs[90].
4. **Comparative Economics:** When considering sotatercept as an addition to background therapy, the incremental cost-effectiveness ratio must be evaluated against established thresholds and alternative treatment options.

As experience with sotatercept in real-world settings accumulates, refinements in patient selection, monitoring protocols, and combination strategies will likely enhance its cost-effectiveness profile. The potential for disease-modifying effects that reduce long-term healthcare utilization and improve productivity could substantially impact the overall economic evaluation of sotatercept in PAH management.

### 9.1.5 Biomarkers and Predictors of Response to Sotatercept Therapy

As precision medicine advances in PAH management, identifying reliable biomarkers and predictors of treatment response becomes increasingly important for optimizing therapeutic strategies. For novel therapies like sotatercept, biomarkers may serve multiple purposes: patient selection, dose optimization, monitoring of treatment effects, and early identification of adverse events.

#### 9.1.5.1 Biomarker Development in PAH :

Various categories of biomarkers have been investigated in PAH, reflecting the complex pathobiology of the disease:

1. **Cardiac Biomarkers:** NT-proBNP and BNP are the most established biomarkers in PAH, reflecting right ventricular wall stress and strongly correlating with hemodynamics, functional capacity, and prognosis[91].
2. **Markers of Vascular Dysfunction:** Endothelin-1, asymmetric dimethylarginine (ADMA), and vascular endothelial growth factor (VEGF) reflect various aspects of endothelial function and vascular homeostasis[92].
3. **Inflammatory Markers:** Cytokines (IL-1, IL-6, TNF-α), chemokines, and C-reactive protein indicate the inflammatory component of PAH[93].
4. **Markers of Oxidative Stress:** Isoprostanes, malondialdehyde, and altered antioxidant capacity reflect oxidative damage in PAH[94].
5. **Metabolic Markers:** Alterations in glucose metabolism, fatty acid oxidation, and mitochondrial function markers indicate metabolic dysregulation in PAH[95].
6. **Genetic and Epigenetic Markers:** BMPR2 mutations, other genetic variants, and epigenetic modifications may indicate disease susceptibility and potentially treatment response[26].
7. **MicroRNAs:** Various circulating miRNAs have shown potential as diagnostic and prognostic biomarkers in PAH[96].

The development of reliable biomarkers for PAH faces several challenges, including disease heterogeneity, small patient populations, analytical variability, and the need for validation in diverse cohorts. Multimarker panels and integration with clinical parameters may provide more robust predictive value than single biomarkers.

#### 9.1.5.2 Potential Predictive Biomarkers for Response to Sotatercept :

Given sotatercept's mechanism of action targeting the TGF-β/BMP signaling pathway, several categories of biomarkers may be particularly relevant for predicting and monitoring response to this therapy:

**TGF-β/BMP Pathway Components**[55,63,80]**:**

1. **Activin A and Other Ligands:** Baseline levels of activin A, GDF8, GDF11, and other ligands targeted by sotatercept may predict response magnitude, with higher levels potentially indicating greater benefit.
2. **BMPR2 Expression:** Variations in BMPR2 expression or function, whether due to mutations or other factors, may influence response to pathway modulation with sotatercept.
3. **Smad Signaling:** Markers of Smad1/5/8 versus Smad2/3 pathway activation could reflect the signaling imbalance that sotatercept aims to correct.
4. **Pathway Antagonists:** Levels of endogenous BMP antagonists like gremlin, noggin, or follistatin may modify sotatercept's effects.

1. **Hemoglobin Response:** Early changes in hemoglobin levels reflect target engagement and may correlate with clinical response, though this relationship requires further characterization.
2. **Early NT-proBNP Changes:** Rapid reductions in NT-proBNP after sotatercept initiation may predict subsequent clinical and hemodynamic improvements.
3. **Pathway-Specific Biomarkers:** Changes in circulating TGF-β/BMP pathway components after treatment initiation may indicate biological response.

Research into predictive biomarkers for sotatercept response is still emerging, and prospective studies specifically designed to identify and validate such markers are needed. Ideally, biomarker development would enable clinicians to select patients most likely to benefit from sotatercept and to optimize treatment regimens based on individual patient characteristics.

# 10 Discussion:

Sotatercept, marketed under the name “Winrevair,” is an innovative treatment designed to treat PAH through the signaling process. This fusion protein, which acts as a “ligand trap,” is composed of the extracellular domain of the human activin receptor type IIA (ActRIIA) fused to the Fc portion of an antibody. This structure allows sotatercept to bind to and neutralize circulating pro-proliferative ligands, mainly activins and growth differentiation factors (GDFs), which stimulate the harmful Smad2/3 pathway.

The action of sotatercept, which consists of sequestering these ligands, has two main effects:

Direct inhibition, through it’s ability to directly inhibit the pro-proliferative Smad2/3 pathway.

Indirect restoration, entering in competition for a shared intracellular protein known as Smad4. This competition indirectly contributes to strengthening the protective and antiproliferative BMP/Smad1/5/8 signaling pathway.

This molecular rebalancing results in physiological benefits, including inhibition of vascular cell proliferation, reduction of inflammation, and prevention of fibrosis, which is characteristic of remodeling associated with PAH.

Clinical evidence provides decisive insight into the efficacy of the treatment. The results of many trials show that it has a significant and transformative impact on patients.

The results of the clinical trials conducted with sotatercept indicate that it has demonstrated significant and sustained efficacy in patients already receiving standard combination therapy.

Promising results were observed in the PULSAR Phase II clinical trial. Data analysis revealed that injection of sotatercept, resulted in a significant, dose-dependent reduction in PVR, which was the primary endpoint of the study. This reduction amounted to -33.9% corrected compared to placebo in subjects receiving a dose of 0.7 mg/kg of the drug. Statistical analysis of these results revealed a p-value of less than 0.001, which is considered highly significant in terms of clinical research criteria. In addition, improvement in exercise capacity, as assessed by the six-minute walk distance (6MWD), was observed, as well as a reduction in NT-proBNP, a key biomarker of right ventricular stress. The improvement in circulatory function was induced by a reduction in mPAP, suggesting structural anti-remodeling effects rather than simple vasodilation.

In the phase III clinical trial called “STELLAR,” it was established that the expected benefits were confirmed in a larger population that had received a significant number of prior treatments. The results of the clinical study conducted with sotatercept reveal that it met its primary endpoint. In fact, a corrected increase in the distance walked by the patient in 6 minutes (6MWD) compared to placebo was observed, with a result of +40.8 meters ($p <$

0.001). This outcome represents a major advance in the field of adjuvant therap. The study also achieved positive results in eight of the nine secondary endpoints. Among these results, there was a significant reduction in the risk of clinical worsening or death.

Open-label extension studies (PULSAR OLE and SOTERIA) have shown that these clinical and hemodynamic benefits are not only durable but continue to improve over time. These results provide strong evidence of a true disease-modifying effect.

The safety profile of sotatercept is unique and related to its mechanism of action. In most cases, the most frequently observed side effects include a moderate increase in hemoglobin levels, thrombocytopenia (a decrease in the number of blood platelets), and the formation of telangiectasias (the presence of small dilated blood vessels on the skin). Epidemiological analyses have revealed that the rates of treatment discontinuation due to these side effects were low, and that the overall benefit-risk ratio was considered very favorable.

The introduction of sotatercept represents a major paradigm shift in the treatment of PAH. This treatment constitutes a major advance in the field of vascular disease management, targeting not only the symptoms resulting from vasoconstriction, but also acting on the fundamental cause of vascular remodeling. The remarkable efficacy of this drug as an adjunctive treatment significantly changes the definition of “maximum medical therapy” and establishes a new, more rigorous standard for clinical response. The improvement in right ventricular function achieved by sotatercept is a major focus of this therapy.

# 11 Conclusion:

In conclusion, sotatercept represents a major advance in the management of pulmonary arterial hypertension, fundamentally changing the therapeutic landscape. Unlike conventional treatments, which mainly provide symptomatic relief through vasodilation, sotatercept offers a new disease-modifying approach. By acting as a ligand trap to restore balance in the TGF-β/BMP signaling pathway, this drug represents a major advance in the treatment of PAH, directly targeting the underlying vascular remodeling that underlies the pathogenesis of this disease.

Results from pivotal trials have demonstrated profound and consistent efficacy, with significant improvements in hemodynamics, exercise capacity, and right ventricular function, even in patients who have already received multiple treatments. These observations validate the study's innovative mechanism. Sotatercept not only sets a new benchmark in clinical benefit, but also heralds a new era in the management of PAH. This therapeutic approach is distinguished by a refocusing of attention on the potential to modify the very structure of the disease, thereby providing new hope and the opportunity for a significant improvement in long-term outcomes for patients affected by this devastating condition.

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Introduction: Pulmonary arterial hypertension (PAH) is a serious disease characterised by elevated pulmonary arterial pressure (mPAP >20 mmHg) associated with pulmonary vascular resistance >2 Wood units. This progressive disease is defined by pulmonary vascular remodelling and, without effective treatment, leads to right heart failure and death. Its prevalence is approximately 3 cases per 100,000 people, with a predominance in women (ratio 2.3:1).

PAH results from an imbalance between vasodilator (NO, prostacyclins) and vasoconstrictor (endothelin-1) signalling pathways, but above all from a fundamental dysregulation of the TGF-β superfamily pathways. Mutations or reduced expression of the BMPR2 receptor lead to a decrease in protective BMP/Smad1/5/8 signalling, favouring overactivation of the TGF-β/activin/Smad2/3 pathway, which promotes cell proliferation, inflammation and vascular fibrosis.

Conventional therapies (PDE5 inhibitors, endothelin receptor antagonists, prostacyclin analogues, soluble guanylate cyclase stimulators) mainly target vasoconstriction and not the underlying vascular remodelling. Despite advances in triple therapy, these treatments remain symptomatic, slowing progression without fundamentally altering the course of the disease, with mortality rates remaining high (7% at one year for stages I-II, 19% for stages III-IV).

Sotatercept (Winrevair) is an innovative fusion protein composed of the extracellular domain of the type IIA activin receptor (ActRIIA) linked to the Fc portion of human IgG1. It acts as a 'ligand trap' selectively sequestering activins A and B, GDF8 (myostatin) and GDF11, thereby inhibiting the pro-proliferative Smad2/3 pathway. This mechanism restores balance with the anti-proliferative BMP/Smad1/5/8 pathway, directly targeting the fundamental pathological process of PAH.

The PULSAR trial (phase II) showed a significant reduction in pulmonary vascular resistance (-33.9%, $p<0.001$) and an improvement in 6-minute walk distance (+29.4m, $p=0.03$). The STELLAR study (phase III) confirmed these results with a placebo-corrected improvement of +40.8 metres in walking distance ($p<0.001$), as well as a significant improvement in 8 secondary endpoints including pulmonary vascular resistance, NT-proBNP levels, functional class and time to clinical worsening or death. These benefits were observed even in patients already receiving optimal dual or triple therapy.

The main adverse effects included elevated haemoglobin, moderate thrombocytopenia, cutaneous telangiectasia and epistaxis, which were generally well tolerated with a low treatment discontinuation rate.

Sotatercept represents a paradigm shift in the treatment of PAH by targeting not only the symptoms but also the fundamental mechanism of vascular remodelling. Its disease-modifying potential could transform the prognosis of this condition, which until now has been considered progressively fatal despite current treatments. This innovative, recently approved therapeutic approach opens up new prospects for significantly improving long-term outcomes in patients with PAH.

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