01 July 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Winrevair (Sotatercept)

Treatment of pulmonary arterial hypertension

EU/3/20/2369

Sponsor: Merck Sharp & Dohme B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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1. Product and administrative information

Product	
Designated active substance(s)	Sotatercept
Other name(s)	Winrevair
International Non-Proprietary Name	Sotatercept
Tradename	Winrevair
Orphan condition	Treatment of pulmonary arterial hypertension
Sponsor's details:	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	IDEA Innovative Drug European Associates (Ireland) Limited
COMP opinion	05 November 2020
EC decision	09 December 2020
EC registration number	EU/3/20/2369
Post-designation procedural history	
Transfer of sponsorship	Transfer from IDEA Innovative Drug European Associates (Ireland) Limited to Merck Sharp & Dohme B.V. – EC decision of 25 April 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Patrick Vrijlandt / Maria Concepcion Prieto Yerro
Applicant	Merck Sharp & Dohme B.V.
Application submission	04 October 2023
Procedure start	26 October 2023
Procedure number	EMA/H/C/005647/0000
Invented name	Winrevair
Proposed therapeutic indication	Winrevair is indicated for the treatment of pulmonary arterial hypertension (PAH) in adult patients on standard of care with WHO Functional Class (FC) II to III, to improve exercise capacity, provide clinical improvement, improve WHO FC and delay disease progression, including to reduce the risk of death and hospitalisation for PAH. Efficacy has been shown in a PAH population including aetiologies of idiopathic and heritable PAH, PAH associated with connective tissue disease, drug or toxin-induced PAH, or PAH associated with congenital heart disease with repaired shunts (see section 5.1). Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Winrevair

CHMP opinion	27 June 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Joao Rocha / Elisabeth Johanne Rook
Sponsor's report submission	30 October 2023
COMP discussion	18-20 June 2024
COMP opinion (adoption via written procedure)	01 July 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing sotatercept was considered justified based on a reduction in pulmonary vascular resistance and improvements in 6-minute walking test in patients treated with the product;
- the condition is life-threatening and chronically debilitating due to progressive dyspnoea and right heart failure, leading to premature death;
- the condition was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sotatercept will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrated significant reduction in pulmonary vascular resistance and improvements in 6-minute walking test when sotatercept was used on top of authorised products. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing sotatercept as an orphan medicinal product for the orphan condition: treatment of pulmonary arterial hypertension.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Pulmonary arterial hypertension (PAH) is a rare progressive disease, which is characterized by an elevation of mean pulmonary artery pressure above 25 mmHg.

The increased pressure is a consequence of the obstruction in pulmonary circulation, which is caused by vasoconstriction and proliferation. The result is a raised pulmonary vascular resistance, which increases the strain on the right ventricle, leading eventually to the right ventricular failure. PAH is a multifactorial disease, to which several factors contribute including genetic mutations (BMPR2), inflammation, potentiated vasoconstriction, and pro-proliferative signalling cascades (endothelin, serotonin). On the other hand, vasodilatory and anti-proliferative pathways (prostacyclin, NO) are diminished.

The clinical severity of PAH is classified according to the WHO system based on functional classes (FC) which range from the mildest FC I to the most severe FC IV. This classification system for PAH is used to assess the impact of the disease on a patient's daily activities and overall quality of life. The FC evaluation is part of the risk assessment of PAH at time of diagnosis and follow up [Humbert, M., et al 2022]. Based on a comprehensive systematic literature review conducted by the Sponsor [BluePrint Orphan 2022], the distribution of functional class at PAH diagnosis is (median, (interquartile range) across 37-51 studies per FC): FC I – 1.8% (0.8%-3.1%); FC II – 20.8% (16.7%-29.6%); FC III – 61.2% (53.0%-70.1%); FC IV- 10.9% (6.6%-13.3%). Of note, percentages do not add to 100 because not all studies reported all functional classes.

The approved therapeutic indication "*Winrevair, in combination with other pulmonary arterial hypertension (PAH) therapies, is indicated for the treatment of PAH in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity (see section 5.1)"* falls within the scope of the designated orphan condition "Treatment of pulmonary arterial hypertension".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

PAH is a debilitating and progressive cardiopulmonary disease, affecting patients of all ages (*Post and Mager, 2015*). In patients with PAH, endothelial dysfunction creates an imbalance, where vasoconstriction, thrombosis, and proliferation of SMCs of the pulmonary arterioles are favoured (*Archer et al, 2010*). Over time, progressive narrowing of the pulmonary vasculature leads to increased pulmonary vascular pressure and resistance, right heart failure, and ultimately death.

In untreated patients, median survival is 2.8 years (*D'Alonzo et al, 1991*) and 5-year survival is 44%. Moreover, with recent advances, PAH remains a progressive disease without a cure, with one-year and three-year mortality at around 8-15% and 31-45%, respectively (*Benza et al, 2012; Humbert et al, 2010*; *Thenappan et al, 2010*). PAH is chronically debilitating for everyday functioning life, and life-threatening disease with cardiac failure at advanced stage of disease progression.

Current PAH treatment has shown to improve exercise tolerance and quality of life and, in some cases, improve the time to clinical worsening and reduce mortality. Nevertheless, these medications target mainly the vasoactive aspect of PAH without effect on the remodelling mechanism, mainly leading to right-heart failure.

Number of people affected or at risk

The sponsor proposes a prevalence estimate of 1.6 per 10,000 persons.

This estimate is slightly higher than the one accepted by the COMP during the initial orphan designation for Sotatercept in 2020, which was approximately 1.4 per 10,000 persons.

For this orphan review procedure, the sponsor presents an updated review of epidemiologic data in the EU including literature and PAH disease registries. The sponsor's estimate is based on the mean value of the reported prevalence rates from the literature (Table 1) multiplied by several correction factors including age and PAH subgroups, undiagnosed subjects and registry coverage (Table 2, sensitivity analysis).

Table 1. Prevalence of PAH in Europe

Country	Source	PAH Prevalence Rate per 1M	PAH Prevalence Rate per 10,000	2022 Country Adult Population	2022 Est. Adult Prevalent Cases
Sweden	SPAHR 2021 [Kjellstrom, B., et al 2021]	48.8	0.49	8,074,000	394
Poland	Kopec 2020 [Kopec, G., et al 2020]	30.8	0.31	30,980,400	954
Latvia	Skride 2018 [Skride, A., et al 2018]	45.7	0.46	1,486,800	68
Germany	Hoeper 2016 [Hoeper, M. M., et al 2016]	25.9	0.26	69,660,200	1,803
Czechia	Jansa 2014 [Jansa, P., et al 2014]	22.4	0.22	8,730,000	196
Spain	Escribano-Subias 2012 [Escribano-Subias, P., et al 2012]	16.0	0.16	38,780,600	620
France	Humbert 2006 [Humbert, M., et al 2006]	15.0	0.15	51,842,000	778
UK	NHS Digital 2021 [NHS Digital 2021]	54.1	0.54	54,178,400	2,933
Switzerland	Mueller-Mottet 2015 [Mueller-Mottet, S., et al 2015]	8.6	0.09	7,197,800	62
Mean Prevalence Rate			0.29		
Median Prevalence Rate			0.26		

Table 2. Sensitivity Analysis

Variable	Assumption	Correction Factor	Prevalence (Number per 10,000)
Base estimate			0.29 (based on mean prevalence estimate from the literature)
PAH subgroups	HPAH and IPAH account for only half of PAH patients	x2	0.58
Age groups	Approximately 15% of EU population is <15 years of age	x1.15	0.667
Undiagnosed subjects	Approximately 21% of PAH patients go undiagnosed for 2 years	x1.21	0.807
Registry coverage	Only 50% of PAH patients captured by regional registries	x2	1.61

Source: [Brown, L. M., et al 2011]

The sponsor states that the proposed prevalence estimate is a worst-case scenario which may overestimate the actual prevalence of PAH in the EU, based on too conservative correction factors used in the sensitivity analysis. This is mostly owing to an expected increase in the proportion of diagnosed subjects and an increase of the registry coverage and subgroups.

While the proposed prevalence estimate of 1.6 per 10,000 persons may be on the conservative end, the COMP accepted the proposed value and notes that it is also in line with previously accepted values in this condition.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

A total of 10 medicines are currently approved in the EU for the treatment of patients with PAH (see Table 3). All these medicines almost exclusively target pathways that either act directly or indirectly to increase blood flow through the pulmonary vasculature (i.e., vasodilators). These medicines largely target three pathways: prostacyclins and prostacyclin receptor agonists (act through cAMP signalling), endothelin-1 pathway and nitric oxide (NO) pathway modulators (act through cGMP signalling). The medicines that interfere with these pathways, administered as monotherapy or in combination, are intended to improve vascular tone by targeting one or more of the dysregulated processes leading to pulmonary vasoconstriction. They have been shown to provide symptomatic improvement to patients with PAH and to slow disease progression to varying degrees. These medicines may reduce mortality, however, there is still limited evidence to suggest that they improve the underlying disease or have a meaningful impact on long-term survival.

Table 3. An Overview of Medicinal Products Authorized in the EU for the Treatment of PAH

Active substance or INN	**Indication**	**Mechanism of action**
Tadalafil Adcirca is a CAP (centrally authorized product)	Treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.	PDE5 inhibitor
Sildenafil Revatio is a CAP	Adults Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. Paediatric population Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary hemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease (see section 5.1).	PDE5 inhibitor
Ambrisentan Volibris is a CAP	Treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease. Treatment of PAH in adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III including use in combination treatment. Efficacy has been shown in IPAH, familial, corrected congenital and in PAH associated with connective tissue disease (see section 5.1).	Endothelin receptor antagonist
Bosentan Tracleer is a CAP	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in: • Primary (idiopathic and heritable) pulmonary arterial hypertension • Pulmonary arterial hypertension secondary to scleroderma without significant interstitial pulmonary disease • Pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology Some improvements have also been shown in patients with pulmonary arterial hypertension WHO functional class II (see section 5.1).	Endothelin receptor antagonist

Active substance or INN	Indication	Mechanism of action
Macitentan Opsumit is a CAP	As monotherapy or in combination, long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).	Endothelin receptor antagonist
Riociguat Adempas is a CAP	Treatment of adult patients with WHO Functional Class (FC) II to III with • inoperable CTEPH, • persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity (see section 5.1). As monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity. Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.	Soluble guanylate cyclase (sGC) stimulator
Epoprostenol Flolan is a NAP (MRP) registered in 12/30 countries Veletri is a NAP (nationally authorized product) (DCP) registered in 13/30 countries	Treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III–IV symptoms to improve exercise capacity.	Prostacyclin analogue
Iloprost Ventavis is a CAP	Treatment of adult patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.	Prostacyclin analogue
Treprostinil Trepulmix is a CAP Remodulin is a NAP (MRP) registered in 24/30 EEA countries	Treatment of adult patients with WHO Functional Class (FC) III or IV and: • inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or • persistent or recurrent CTEPH after surgical treatment to improve exercise capacity.	Prostacyclin analogue

Active substance or INN	Indication	Mechanism of action
Selexipag Uptravi is a CAP	Long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).	Prostacyclin receptor agonist

The 2022 ESC/ERS PAH treatment guidelines recommend the use of a sequential combination of PAH drug therapy including phosphodiesterase 5 (PDE5) inhibitors (PDE5i) or stimulators of soluble guanylate cyclase (sGC), endothelin-1 (ET-1) receptor antagonist (ERA), and prostacyclins with the goal of achieving low risk status for every patient as it results in the best long-term prognosis (see Figure 3) [Galie, N., et al 2019] [Humbert, M., et al 2022].

For initial treatment:

In low- or intermediate-risk patients, initial combination therapy with a PDE5i and an ERA is recommended, with tadalafil combined with ambrisentan or tadalafil with macitentan having the highest recommendation class (ESC/ERS Class I, Level B).

In high-risk patients, the addition of parenteral prostacyclin analogs and either IV epoprostenol or IV/SC treprostinil should be considered (ESC/ERS Class IIa, Level C).

For follow-up treatment:

In low-risk patients, initial treatment (ERA + PDE5i) should be continued.

In patients at intermediate-low-risk despite receiving ERA/PDE5i therapy, either of the following options should be considered:

- adding selexipag (ESC/ERS Class IIa, Level B)
- switching from PDE5i to soluble guanylate cyclase stimulator (sGC) (ESC/ERS Class IIb, Level B).

In patients at intermediate-high or high risk while receiving oral therapies, adding IV epoprostenol or IV/SC treprostinil must be considered as first choice. At the same time, the patient should be referred for lung transplant evaluation. Only for patients considered not suitable for parenteral prostanoids in an individual assessment (older patients, high number of comorbidities, treatment rejection), adding selexipag as first choice or switching from PDE5i to riociguat to optimize oral therapy should be considered.

When the combination of existing PAH treatments, including prostacyclin (epoprostenol or IV/SC treprostinil), has been exhausted, and the patient's condition continues to deteriorate, there is currently no satisfactory pharmaceutical treatment option available. In this case, lung transplantation is a treatment option that is typically considered as a last resort for patients with end-stage PAH.

See Figure 1 for ERS/ESC treatment algorithm for PAH [Humbert, M., et al 2022].

Figure 1. ERS/ESC treatment algorithm for PAH

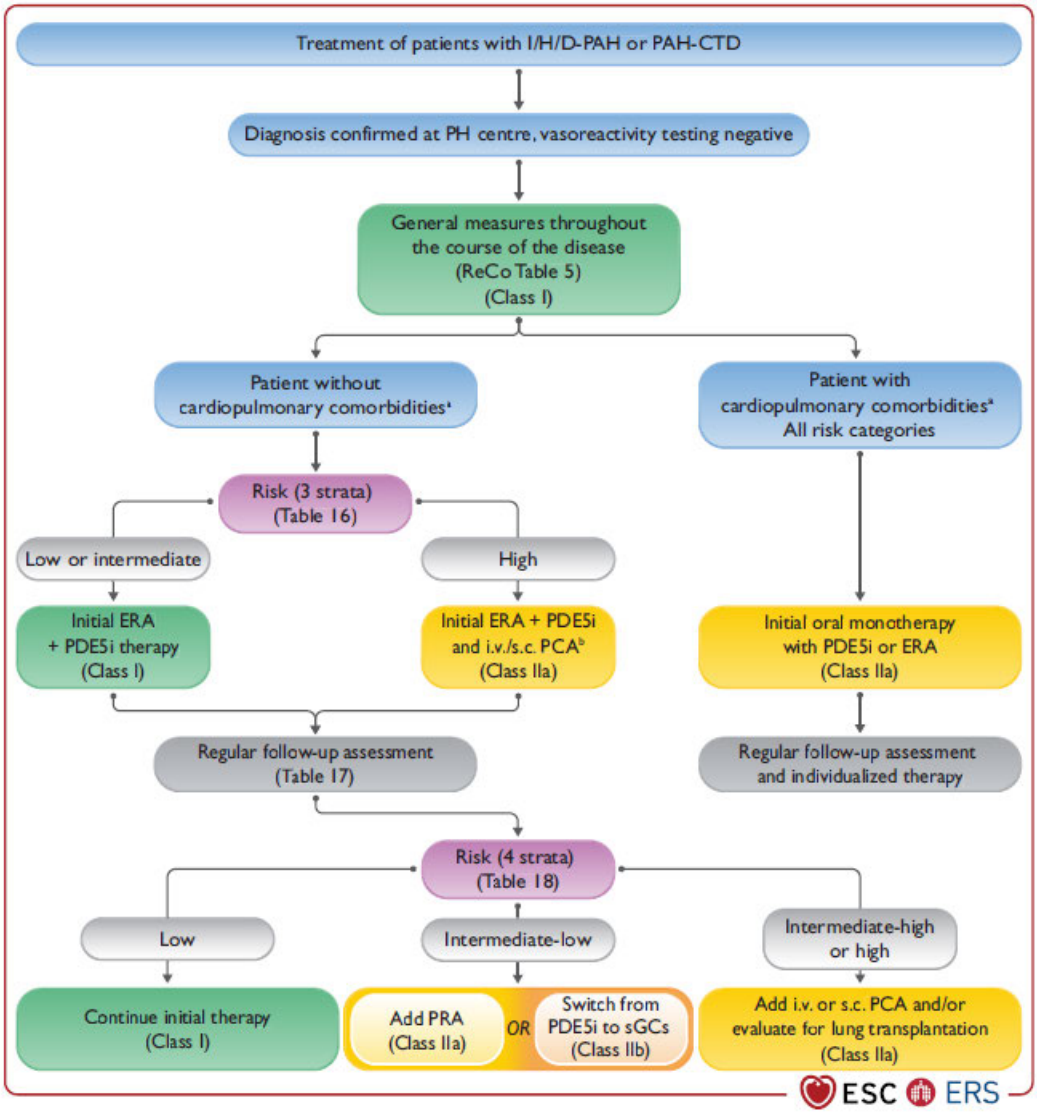


Figure 9 Evidence-based pulmonary arterial hypertension treatment algorithm for patients with idiopathic, heritable, drug-associated, and connective tissue disease-associated pulmonary arterial hypertension. DLCO, Lung diffusion capacity for carbon monoxide; ERA, endothelin receptor antagonist; I/H/D-PAH, idiopathic, heritable, or drug-associated pulmonary arterial hypertension; i.v., intravenous; PAH-CTD, PAH associated with connective tissue disease; PCA, prostacyclin analogue; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension; PRA, prostacyclin receptor agonist; ReCo, recommendation; s.c., subcutaneous; sGCs, soluble guanylate cyclase stimulator. [a]Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease; pulmonary comorbidities may include signs of mild parenchymal lung disease and are often associated with a low DLCO (<45% of the predicted value). [b]Intravenous epoprostenol or i.v./s.c. treprostinil.

Significant benefit

The significant benefit of sotatercept vs currently authorized PAH therapies is mostly based on a claim of improved efficacy. In the sponsor's pivotal study, sotatercept demonstrated significant and clinically meaningful benefit in a broad range of patients, including those who have exhausted combination therapy with all currently authorized medicinal products for PAH. Based on this, the CHMP supported a broad therapeutic indication of the combination use of sotatercept with "other pulmonary arterial hypertension (PAH) therapies".

Sotatercept acts through a novel mechanism of action, which modulates vascular proliferation and thereby addresses a contributing factor in the pathophysiology of PAH. This is different from current standard of care therapies acting through vasodilation.

In support of their claim of improved efficacy over currently authorized medicinal products in PAH, the sponsor presents the efficacy data from their pivotal study (STELLAR). The STELLAR trial was a double-blind phase 3 trial wherein 323 adults with PAH were randomized 1:1 to receive sotatercept or placebo administered subcutaneously (SC) every 3 weeks on top of optimized, stable (≥90 days) background therapy (monotherapy or combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists), (Table 4). Eligible patients had a confirmed diagnosis of PAH (idiopathic, heritable, drug-induced, connective-tissue disease–associated, or after shunt correction) in WHO functional class II or III. The baseline PVR was ≥5 Wood units (≥400 dynes*sec/cm5) by RHC and baseline 6-minute walk distance (6MWD) range was ≥150 and ≤500 meters.

Most participants were receiving either triple (61.3%) or double (34.7%) background PAH therapy, and more than one-third (39.9%) were receiving prostacyclin infusions (Table 4). The proportions of participants in WHO FC II was 48.6% and in WHO FC III was 51.4%.

Table 4. Types of background therapy in pivotal study with sotatercept (STELLAR)

SOC Medications	Placebo (N=160) n (%)	Sotatercept (N=163) n (%)	Total (N=323) n (%)
Prostacyclin Therapy	117 (73.1)	114 (69.9)	231 (71.5)
Prostacyclin IV/SC	65 (40.6)	65 (39.9)	130 (40.2)
Prostacyclin Oral	37 (23.1)	39 (23.9)	76 (23.5)
Prostacyclin Respiratory (Inhalation)	15 (9.4)	10 (6.1)	25 (7.7)
No Prostacyclin Therapy	43 (26.9)	49 (30.1)	92 (28.5)
Monotherapy	4 (2.5)	9 (5.5)	13 (4.0)
PDE5 inhibitor	1 (0.6)	5 (3.1)	6 (1.9)
sGC	1 (0.6)	0 (0.0)	1 (0.3)
ERA	1 (0.6)	2 (1.2)	3 (0.9)
Prostacyclin IV/SC	1 (0.6)	2 (1.2)	3 (0.9)
Double Therapy	55 (34.4)	56 (34.4)	111 (34.4)
ERA+PDE5 inhibitor	38 (23.8)	36 (22.1)	74 (22.9)
ERA+sGC	2 (1.3)	6 (3.7)	8 (2.5)
ERA+Prostacyclin IV/SC	3 (1.9)	4 (2.5)	7 (2.2)
ERA+Prostacyclin Respiratory (Inhalation)	2 (1.3)	0 (0.0)	2 (0.6)
PDE5 inhibitor+Prostacyclin IV/SC	3 (1.9)	5 (3.1)	8 (2.5)
PDE5 inhibitor+Prostacyclin Oral	4 (2.5)	3 (1.8)	7 (2.2)
PDE5 inhibitor+Prostacyclin Respiratory (Inhalation)	0 (0.0)	1 (0.6)	1 (0.3)
Prostacyclin IV/SC+sGC	1 (0.6)	1 (0.6)	2 (0.6)
Prostacyclin Oral+sGC	2 (1.3)	0 (0.0)	2 (0.6)
Triple Therapy	101 (63.1)	98 (60.1)	199 (61.6)
ERA+PDE5 inhibitor+Prostacyclin IV/SC	49 (30.6)	45 (27.6)	94 (29.1)
ERA+PDE5 inhibitor+Prostacyclin Oral	27 (16.9)	27 (16.6)	54 (16.7)
ERA+PDE5 inhibitor+Prostacyclin Respiratory (Inhalation)	9 (5.6)	7 (4.3)	16 (5.0)
ERA+Prostacyclin IV/SC+sGC	8 (5.0)	8 (4.9)	16 (5.0)
ERA+Prostacyclin Oral+sGC	4 (2.5)	9 (5.5)	13 (4.0)
ERA+Prostacyclin Respiratory (Inhalation)+sGC	4 (2.5)	2 (1.2)	6 (1.9)

N = number of subjects in the treatment group or overall. n = number of subjects in the category. Percentages are calculated as (n/N)*100.

IV = intravenous, SC=subcutaneous, PDE5 Inhibitor= phosphodiesterase type 5 inhibitor, sGC= soluble guanylate cyclase, ERA= endothelin receptor antagonist. Prostacyclin includes prostacyclin analogs and prostacyclin receptor analogs.

Source: [P003MK7962: adam-adsl]

Patients were stratified according to baseline WHO FC (II vs. III) and background therapy for PAH (monotherapy or double therapy vs. triple therapy).

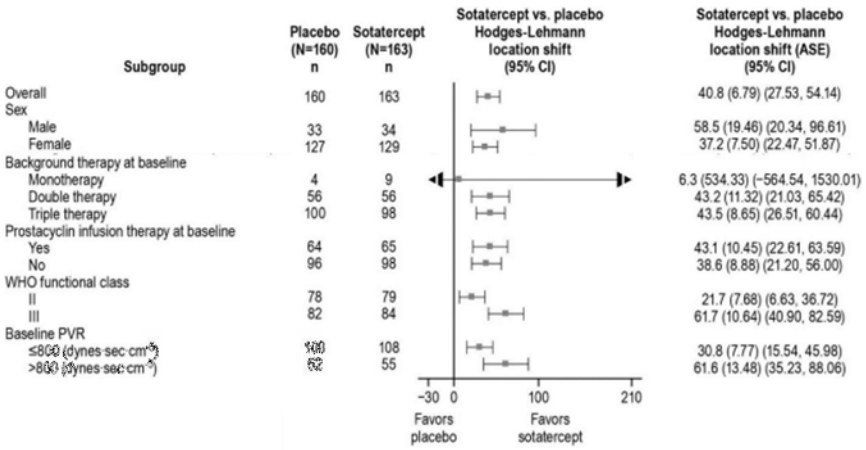
The primary endpoint was the change from baseline at Week 24 in 6MWD. Nine secondary endpoints, tested hierarchically to control for multiplicity included the proportion of patients achieving multicomponent improvement (MCI; defined as increase ≥30 meters in 6MWD, decrease in N terminal pro-B-type natriuretic peptide (NT-proBNP) ≥30% or maintenance/achievement of NT proBNP level <300 ng/L, and improvement of WHO FC or maintenance of WHO FC II) at Week 24; change in PVR, NT-proBNP, and proportion of patients with improved WHO FC at Week 24; time to death or first occurrence of a clinical worsening event; proportion of patients achieving low Risk score at Week 24; and change in three PAH-SYMPACT® domain scores at Week 24.

Several pre-planned subgroup analyses were conducted, including based on background Monotherapy vs. Double vs. Triple combination therapy at baseline for the primary efficacy endpoint and the following secondary endpoints: PVR, NT-proBNP is the sample size at each level of the subcategory ≥10. The sponsor did not conduct further subgroup analyses based on the exact products/product classes included in the respective background Monotherapy vs. Double vs. Triple combination therapy groups due to the too limited sample size in such subgroups and therewith the high level of methodologic uncertainty over true effects.

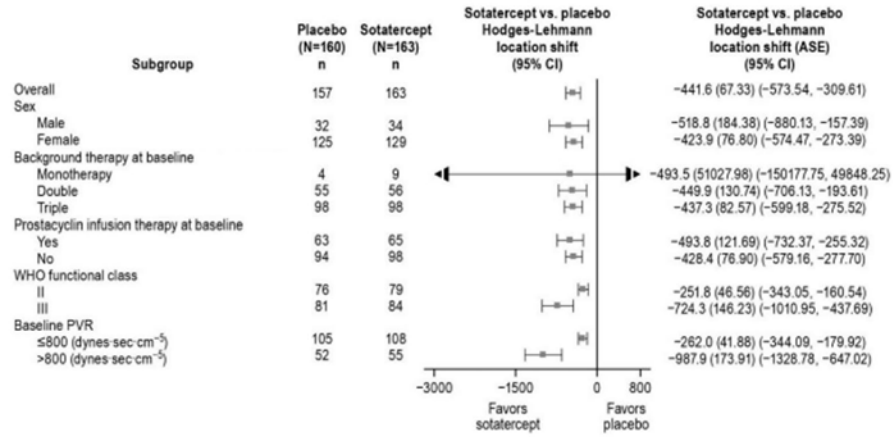
Treatment with sotatercept resulted in a significant improvement in 6MWD from baseline to week 24 as compared to placebo in patients with PAH (WHO Group 1) on background PAH therapy (median: 34.4 m vs. 1.0 m, respectively; median treatment difference (Hodges-Lehmann location shift) of 40.8m (95% CI : 27.53, 54.14); p< 0.001) from baseline levels of 397.6 m and 404.7 m for the sotatercept and placebo group, respectively. The effect was consistent in the prespecified sensitivity analyses using alternative methods of imputation for the 6MWD. The improvement in exercise capacity was further supported by significant improvements in MCI, PVR, NT-proBNP, WHO, TTCW, low-risk score (using simplified French Risk Score) and physical impacts and cardiopulmonary symptoms domain score of PAH-SYMPACT. The treatment effect was a consistent across all prespecified subgroups, including background therapy at baseline (monotherapy, double or triple therapy), baseline PVR (≤ 800, > 800 dynes*sec/cm^5, prostacyclin infusion therapy (y/n), see summarized in Figure 2.

Figure 2. Forrest plot of the Hodges-Lehman location shift of the change from baseline at Week 24

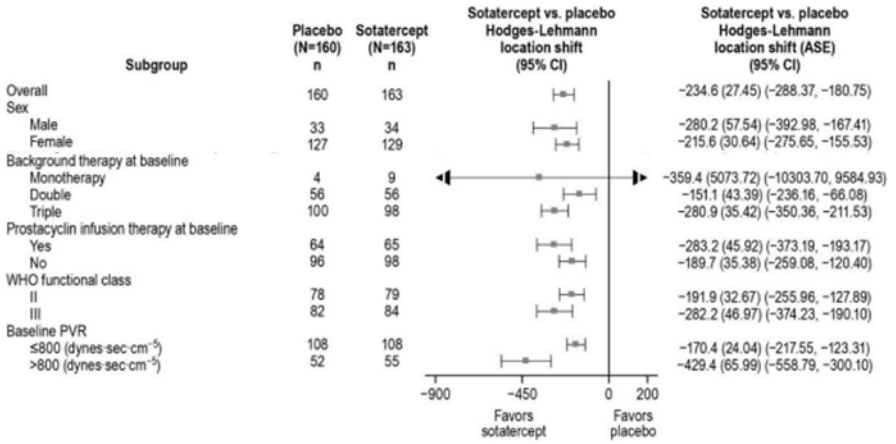
A. 6-MWD



B. NT-proBNP



C. PVR



ASE: asymptotic standard error; CI: confidence interval; Monotherapy or double therapy: receiving either pulmonary arterial hypertension monotherapy or double therapy at baseline; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; s/p: systemic-to-pulmonary; Triple therapy: receiving triple combination pulmonary arterial hypertension therapy at baseline; WHO: World Health Organization; WHO functional class II: slight limitation of activity (ordinary activities cause some symptoms); WHO functional class III: marked limitation of activity (less than ordinary activity causes symptoms)

The COMP concluded that the claim for improved efficacy can be supported based on the efficacy data of the pivotal clinical trial which included a significant number of patients who have exhausted combination therapy with all currently authorized medicinal products. This data was also the basis for the broad therapeutic indication wording of sotatercept which allows combination use with other currently authorized pulmonary arterial hypertension (PAH) therapies.

4. COMP position adopted on 01 July 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of pulmonary arterial hypertension (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to progressive dyspnoea and right ventricular heart failure, leading to premature death;

- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Winrevair is of significant benefit to those affected by the orphan condition is established. The sponsor has provided clinical data that demonstrated a significant reduction in pulmonary vascular resistance and improvements in 6-minute walking test when Winrevair was used in addition to other authorized pulmonary arterial hypertension combination therapies. The Committee considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied.
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Winrevair, sotatercept, for treatment of pulmonary arterial hypertension (EU/3/20/2369) is not removed from the Community Register of Orphan Medicinal Products.