Sotatercept (pulmonary arterial hypertension, WHO) functional class IV)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A26-12 Version: 1.0 Status: 07 May 2026 DOI: 10.60584/A26-12_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Sotatercept (pulmonale arterielle Hypertonie, WHO-Funktionsklasse IV) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Sotatercept (pulmonary arterial hypertension, WHO) functional class IV) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

16 February 2026

Internal Project No.

A26-12

DOI-URL

https://doi.org/10.60584/A26-12_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
Email: info@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Sotatercept (pulmonary arterial hypertension, WHO) functional class IV); Benefit assessment according to §35a SGB V; Extract [online]. 2026 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A26-12_en.

Keywords

Sotatercept, Pulmonary Arterial Hypertension, Benefit Assessment, NCT04896008

Medical and scientific advice

- Thomas O. F. Wagner

IQWiG thanks the medical and scientific advisor for their contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback of persons concerned was received within the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Philip Böhler
- Annalena Dunkel
- Leonie Eilers
- Judith Kratel
- Mattea Patt
- Daniela Preukschat
- Veronika Schneck
- Claudia Selbach
- Pamela Wronski

Part I: Benefit assessment

I Table of contents

Page

I List of tables I.3
I List of figures I.4
I List of abbreviations I.5
I 1 Executive summary of the benefit assessment I.1
I 2 Research question I.7
I 3 Information retrieval and study pool I.10
I 3.1 Evidence provided by the company I.10
I 3.2 Assessment of the evidence presented by the company I.16
I 3.2.1 Missing data on the implementation of the ACT I.16
I 3.2.2 Further limitations of the analyses presented in the ZENITH study I.18
I 4 Results on added benefit I.21
I 5 Probability and extent of added benefit I.22
I 6 References for English extract I.23

I List of tables[2]

Page

Table 2: Research question for the benefit assessment of sotatercept I.2
Table 3: Sotatercept – probability and extent of added benefit I.5
Table 4: Research question for the benefit assessment of sotatercept I.7
Table 5: Characteristics of the study included by the company – RCT, direct comparison: sotatercept vs. placebo I.11
Table 6: Characteristics of the intervention – RCT, direct comparison: sotatercept vs. placebo I.13
Table 7: Sotatercept – probability and extent of added benefit I.22

[2] Table numbers start with '2' as numbering follows that of the full dossier assessment.

I List of figures

Page

Figure 1: Design of the ZENITH study [7] ..... **Fehler! Textmarke nicht definiert.**

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ERA	endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PAH	pulmonary arterial hypertension
PCA	prostacyclin analogues
PDE5I	phosphodiesterase-5 inhibitors
PRA	prostacyclin receptor agonist
RCT	randomised controlled trial
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management
SGB	Sozialgesetzbuch (Social Code Book)
sGC	soluble guanylate cyclase

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sotatercept. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 16 February 2026.

Research question

The aim of this report is to assess the added benefit of sotatercept in combination with other pulmonary arterial hypertension (PAH) therapies in comparison with epoprostenol in combination with endothelin receptor antagonists (ERAs): (ambrisentan, bosentan, macitentan) and phosphodiesterase-5 inhibitors (PDE5I: sildenafil, tadalafil) as appropriate comparator therapy (ACT) in adult patients with PAH with World Health Organization (WHO) functional class IV.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of sotatercept

Therapeutic indication	ACT[a]
Adults with WHO functional class IV PAH	Epoprostenol in combination with ERAs (ambrisentan, bosentan, macitentan) and PDE5is (sildenafil, tadalafil)[b, c]

a. Presented is the ACT specified by the G-BA.
b. No drugs other than the PCA epoprostenol are approved for the treatment of patients with PAH with WHO functional class IV. According to the G-BA, the off-label use of a combination therapy with an ERA and PDE5I, in addition to the approved epoprostenol, is regarded as the therapy standard in the therapeutic indication under assessment and is generally to be preferred to monotherapy with drugs containing the active substance epoprostenol that have previously been approved for the therapeutic indication (Section 6(2), sentence 3, point 2 of the AM-NutzenV).
c. Further comments from the G-BA:

- The guideline recommends a combination therapy comprising ERA, PDE5I and PCA for the treatment of patients with WHO functional class IV PAH. According to feedback from clinical experts, this treatment regimen currently represents the therapy standard for the majority of patients in the considered indication. Where study participants are receiving combination therapy without epoprostenol, the unsuitability of these patients for treatment with epoprostenol must be documented and discussed in the dossier of the benefit assessment.
- It is assumed that combination therapies are usually applied in this therapeutic indication. Furthermore, it is assumed that all patients in both study arms will have access to the continuation of treatment options approved for less serious WHO functional classes, or that these treatment options will be initiated in case of a corresponding therapeutic indication.
- It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
- In principle, a lung transplant or a heart-lung transplant is a treatment option for patients with WHO functional class IV. In view of the fact that the possibility of a lung transplant is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplant cannot be assumed to be a standard treatment option for patients in the given therapeutic indication.
- There are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic interventions in the sense of the Remedies Directive (physical therapy, e.g. physiotherapy, exercise treatment, respiratory therapy) if indicated, should be made available to patients in both arms of the study in addition to drug therapy.

ERA: endothelin receptor antagonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogues; PDE5I: phosphodiesterase-5 inhibitors; WHO: World Health Organization

In its dossier, the company refers to consultations held on 17 June 2025 and 1 December 2025. In both consultations, the G-BA determined the ACT specified in Table 2 (hereinafter: epoprostenol + ERA + PDE5I). The company did not follow this ACT specified by the G-BA, but instead considered an individually optimized drug treatment, taking into account previous treatments and health status, choosing from ERA (ambrisentan, bosentan, macitentan), PDE5I (sildenafil, tadalafil), prostacyclin analogues (PCA: iloprost, treprostinil, epoprostenol), selective prostacyclin receptor agonists (PRA: selexipag) and soluble guanylate cyclase stimulators (sGC stimulators: riociguat) as the ACT. It further states that two subpopulations with correspondingly different treatment options should be assumed to provide an adequate representation of a possibly available treatment escalation.

This benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the G-BA's ACT did not result in an exclusion of potentially relevant studies during the company's information retrieval. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomised controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

Concurring with the company, the check of completeness of the study pool identified the RCT ZENITH comparing sotatercept with placebo, each in addition to background PAH therapy, as potentially relevant study. For the assessment of the added benefit of sotatercept, the company used the subpopulation of patients with WHO functional class IV, regardless of their background treatment. Based on the available information on the background therapy, it is unclear whether the ZENITH study includes a relevant subpopulation for this benefit assessment.

Evidence presented by the company – ZENITH study

The ZENITH study is a completed, multicentre, double-blind RCT comparing sotatercept with placebo, each in addition to background PAH therapy, in adults with PAH WHO functional class III or IV and at high risk of mortality.

The study included adult patients with PAH- (WHO group 1). Patients had to have symptomatic PAH WHO functional class III or IV, a Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2 risk score of ≥ 9, and they had to be clinically stable.

The study included a total of 173 patients who were randomly allocated in a 1:1 ratio to treatment with sotatercept or placebo. Randomisation was stratified by REVEAL Lite 2.0 risk score (9 to 10 vs. ≥ 11) and PAH subtype (with associated connective tissue disease vs. without associated connective tissue disease). A total of 44 patients were classified as WHO functional class IV in accordance with the therapeutic indication relevant to this dossier assessment (sotatercept arm: n = 20, placebo arm: n = 24).

Treatment with sotatercept was largely in compliance with the Summary of Product Characteristics (SmPC). The specified background PAH therapy in the ZENITH study was a dual or triple combination therapy, as determined by the investigator, consisting of at least two drugs from different drug classes, choosing from ERA, PDE5I, sGC stimulators, PRA and/or PCA. Patients were required to have been receiving the maximum tolerated dose, as determined by the investigator, at a stable dose for ≥ 30 days prior to screening and were to continue this dose throughout the study, with a dose adjustment of up to 10% being permitted for parenteral prostacyclins. Drug treatment of chronic diseases other than PAH was permitted at a stable dose, regardless of the drugs used.

The primary outcome of the ZENITH study was the time to occurrence of the first event in a composite outcome comprising hospitalization for ≥ 24 hours due to worsening PAH, lung transplant or death from any cause. Further patient-relevant outcomes were recorded in the categories mortality, morbidity, health-related quality of life and side effects.

Assessment of the evidence presented by the company

Missing data on the implementation of the ACT

For the present therapeutic indication, the G-BA determined a triple therapy with epoprostenol + ERA + PDE5I as the ACT. The comparator therapy in the ZENITH study was placebo under the continuation of an existing dual or triple combination therapy with at least two drugs from different drug classes, choosing from ERA, PDE5I, sGC stimulators, PCA and/or PRA. Whilst this includes all drugs specified in the G-BA's ACT, it does not mandate a triple therapy with epoprostenol + ERA + PDE5I for all patients, but also permits dual therapies and other drug classes (sGC stimulators, PRA and PCA other than epoprostenol). The comparator therapy in the ZENITH study is therefore broader than the G-BA's ACT.

The company's dossier does not provide any information on how many patients in the ZENITH study received triple therapy with epoprostenol (or another parenteral PCA). At least 45% of patients in the subpopulation with WHO functional class IV did not receive intravenous PCA therapy and thus no epoprostenol. The ACT specified by the G-BA was therefore not implemented for a relevant proportion of patients.

In accordance with the G-BA's notes on the ACT, the unsuitability of epoprostenol must be documented and discussed in the dossier for study participants receiving combination therapy without epoprostenol. This was not done. Overall, the company's dossier does not indicate how many patients who did not receive triple therapy with epoprostenol (or another parenteral PCA) would not have been eligible for it.

This means that no suitable data were available for the comparison of sotatercept with the G-BA's comparator therapy.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of sotatercept in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of sotatercept.

Table 3: Sotatercept – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with WHO functional class IV PAH	Epoprostenol in combination with ERAs (ambrisentan, bosentan, macitentan) and PDE5is (sildenafil, tadalafil)[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.

b. No drugs other than the PCA epoprostenol are approved for the treatment of patients with PAH with WHO functional class IV. According to the G-BA, the off-label use of a combination therapy with an ERA and PDE5I, in addition to the approved epoprostenol, is regarded as the therapy standard in the therapeutic indication under assessment and is generally to be preferred to monotherapy with drugs containing the active substance epoprostenol that have previously been approved for the therapeutic indication (Section 6(2), third sentence, point 2 of the AM-NutzenV).

c. Further comments from the G-BA:

- The guideline recommends a combination therapy comprising ERA, PDE5I and PCA for the treatment of patients with PAH in WHO functional class IV. According to feedback from clinical experts, this treatment regimen currently represents the therapy standard for the majority of patients in the considered indication. Where study participants are receiving combination therapy without epoprostenol, the fact that these individuals are not suitable for treatment with epoprostenol must be documented and discussed in the dossier of the benefit assessment.
- It is assumed that combination therapies are generally used in this therapeutic indication. Furthermore, it is assumed that all patients in both study arms will have access to the continuation of the treatment options approved for less serious WHO functional classes, or that these treatment options will be initiated in case of a corresponding therapeutic indication.
- It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
- In principle, a lung transplant or a heart-lung transplant is a treatment option for patients with WHO functional class IV. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication.
- There are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic measures in the sense of the Remedies Directive (physical therapy, e.g. physiotherapy, if indicated, should be made available to patients in both arms of the study in addition to drug therapy.

ERA: endothelin receptor antagonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogues; PDE5I: phosphodiesterase-5 inhibitors; WHO: World Health Organization

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) 'proof', (2) 'indication', (3) 'hint', or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or lesser benefit). For further details see [1,2].

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of sotatercept in combination with other PAH therapies in comparison with epoprostenol in combination with ERAs: (ambrisentan, bosentan, macitentan) and PDE5I (PDE5I: sildenafil, tadalafil) as ACT in adult patients with PAH with World Health Organization (WHO) functional class II to IV.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of sotatercept

Therapeutic indication	ACT[a]
Adults with WHO functional class IV PAH	Epoprostenol in combination with ERAs (ambrisentan, bosentan, macitentan) and PDE5is (sildenafil, tadalafil)[b, c]

a. Presented is the ACT specified by the G-BA.
b. No drugs other than the PCA epoprostenol are approved for the treatment of patients with PAH with WHO functional class IV. According to the G-BA, the off-label use of a combination therapy with an ERA and PDE5I, in addition to the approved epoprostenol, is regarded as the therapy standard in the therapeutic indication under assessment and is generally to be preferred to monotherapy with drugs containing the active substance epoprostenol that have previously been approved for the therapeutic indication (Section 6(2), sentence 3, point 2 of the AM-NutzenV).
c. Further comments from the G-BA:

- The guideline recommends a combination therapy comprising ERA, PDE5I and PCA for the treatment of patients with PAH in WHO functional class IV. According to feedback from clinical experts, this treatment regimen currently represents the therapy standard for the majority of patients in the considered indication. Where study participants are receiving combination therapy without epoprostenol, the fact that these individuals are not suitable for treatment with epoprostenol must be documented and discussed in the dossier of the benefit assessment.
- It is assumed that combination therapies are generally used in this therapeutic indication. Furthermore, it is assumed that all patients in both study arms will have access to the continuation of the treatment options approved for less serious WHO functional classes, or that these treatment options will be initiated in case of a corresponding therapeutic indication.
- It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
- In principle, a lung transplant or a heart-lung transplant is a treatment option for patients with WHO functional class IV. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication.
- There are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic measures in the sense of the Remedies Directive (physical therapy, e.g. physiotherapy, if indicated, should be made available to patients in both arms of the study in addition to drug therapy.

ERA: endothelin receptor antagonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogues; PDE5I: phosphodiesterase-5 inhibitors; WHO: World Health Organization

In its dossier, the company refers to consultations held on 17 June 2025 [3] and on 01 December 2025 [4]. In both consultations, the G-BA identified the ACT set out in Table 4 (hereinafter: epoprostenol + ERA + PDE5I). The company did not follow this ACT specified by the G-BA, but instead considered an individually optimized drug treatment, taking into account previous treatments and health status, choosing from ERA (ambrisentan, bosentan, macitentan), PDE5I (sildenafil, tadalafil), (PCA: iloprost, treprostinil, epoprostenol), selective PRAs (PRA: selexipag) and soluble guanylate cyclase stimulators (sGC stimulators: riociguat) as the ACT. It further states that, in order to adequately reflect any further treatment escalation that may be possible, two subpopulations should be assumed, for which it considers different treatment options as ACTs:

- Subpopulation A: adults with PAH in WHO functional class IV who might still receive a treatment escalation:
  - epoprostenol in combination with continued background therapy with an ERA (ambrisentan, bosentan, macitentan) and/or a PDE5I (sildenafil, tadalafil) or an sGC stimulator (riociguat)
- Subpopulation B: adults with PAH in WHO functional class IV who cannot receive treatment escalation with other PAH therapies:
  - continuation of individualized treatment, choosing from the following therapies: ERA (ambrisentan, bosentan, macitentan), PDE5I (sildenafil, tadalafil), PCA (iloprost, treprostinil, epoprostenol), PRA (selexipag) and sGC stimulator (riociguat)

The company justified its deviation from the G-BA's ACT on the grounds that treatment with epoprostenol + ERA + PDE5I, which the G-BA specified as the ACT, is only suitable for those patients in this therapeutic indication who are still eligible for treatment escalation. According to the company, patients with PAH often receive individualized treatment – making full use of all drug classes listed in the currently valid guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) [5] – even before the disease progresses to WHO functional class IV. This was in line with the G-BA's specification of the ACT in the benefit assessment procedure for sotatercept in PAH in WHO functional classes II to III, which involves individualized treatment choosing from ERA, PDE5I, PCA, selective PRA and sGC stimulators [6]. The company also refers to the minutes of the consultation and the note contained therein regarding the ACT (see Table 4), according to which the continuation of therapy options already approved for less serious PAH WHO functional classes are available or should be initiated where there is a corresponding indication. Furthermore, the company states that the main factors limiting the use of maximally intensified PAH treatment are tolerability and contraindications, which is why not all patients can receive triple therapy. According to the company, patients in WHO functional classes II and III who switched from a PDE5I to an sGC stimulator in an on-label setting will not be switched back to a PDE5 inhibitor in the event of

progression to WHO functional class IV. At the time point of progression to WHO functional class IV, PAH treatment often already includes parenteral PCA, meaning that epoprostenol is generally no longer an option for such patients, unless they are already receiving it. Furthermore, according to the company, some patients refuse treatment with epoprostenol on principle because of the complex and restrictive nature of the intravenous route of administration.

This benefit assessment was conducted in comparison with the ACT specified by the G-BA. The company's deviation from the G-BA's ACT did not result in an exclusion of potentially relevant studies during the company's information retrieval. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This deviated from the company's inclusion criteria, which considered studies irrespective of the study duration.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on sotatercept (status: 15 December 2025)
- Bibliographical literature search on sotatercept (last search on 08 January 2026)
- Search of trial registries / trial results databases for studies on sotatercept (last search on 13 January 2026)
- Search on the G-BA website for sotatercept (last search on 13 January 2026)

To check the completeness of the study pool:

- search in trial registries for studies on sotatercept (last search on 25 February 2026); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool identified the RCT ZENITH [7-12] comparing sotatercept with placebo, each in addition to background PAH therapy, as potentially relevant study. The company uses the subpopulation of patients with WHO functional class IV, regardless of their background therapy, to assess the added benefit of sotatercept in adults with PAH in WHO functional class IV who are no candidates for therapeutic escalation with other PAH therapies. With regard to adults with PAH in WHO functional class IV who are still candidates for treatment escalation, the company states that it has not identified any RCTs. Based on the available information, it is unclear whether the STELLAR study contains a relevant subpopulation for the present benefit assessment.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of sotatercept in comparison with the ACT. Below, the ZENITH study is first described and then the lack of suitability of the data presented for the benefit assessment is justified.

I 3.1 Evidence provided by the company

Design of ZENITH

Table 5 and Table 6 describe the ZENITH study presented by the company for the benefit assessment.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: sotatercept vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ZENITH	RCT, double-blind, parallel	Adults (18-75 years) with symptomatic PAH (WHO group I) with a high risk of mortality[b, c] ▪ WHO functional class III or IV ▪ REVEAL Lite 2 risk score of ≥ 9 ▪ clinically stable	Sotatercept (N = 86) placebo (N = 87) subpopulation analysed by the company[d]: sotatercept (N = 20) placebo (n = 24)	Screening: up to 4 weeks treatment: until the primary outcome is reached, unacceptable toxicity, physician's decision, withdrawal of consent, loss to follow-up occurs, or end of the study[e] follow-up[f]: 8 weeks after the last dose	53 study centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, Mexico, Netherlands, Spain, United Kingdom, USA 12/2021–02/2025 data cuts: 26 July 2024 (interim analysis)[g] 06 June 2025 (final analysis at the end of the study)[k]	Primary: time to death, lung transplant or hospitalization (≥ 24 hours) due to worsening PAH secondary: mortality, morbidity, health-related quality of life, AEs

Table 5: Characteristics of the study included by the company – RCT, direct comparison: sotatercept vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company in Module 4.
b. The study included patients with idiopathic PAH, heritable PAH, drug/toxin-induced PAH, PAH associated with connective tissue disease, or PAH associated with simple, congenital systemic-to-pulmonary shunts.
c. Documented diagnosis of PAH by right heart catheterization. A right heart catheterization performed during screening had to fulfil the following criteria: pulmonary vascular resistance of ≥ 5 WU and a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure of ≤ 15 mmHg.
d. Patients with WHO functional class IV.
e. Following hospitalization (≥ 24 hours) due to worsening PAH or end of the study (whichever occurred first), patients in both study arms were eligible to transfer to the SOTERIA extension study and received sotatercept as part of this study; however, a transfer following hospitalization due to worsening PAH was only permitted from Amendment 2 of the study protocol of 29 June 2023.
f. Follow-up was conducted in patients who discontinued the study prematurely, underwent a lung transplant or did not transfer into the SOTERIA extension study. Irrespective of this, mortality data was also recorded beyond the last visit up to the data cut.
g. Interim analysis, planned for the point in time at which approx. 59 primary outcome events had occurred and a median follow-up period of at least 6 months had elapsed.
h. The study ended (last patient, last visit) on 18 February 2025. The final data cut with simultaneous database lock, took place on 6 June 2025. Mortality data were recorded until the database lock. According to the company, safety data were submitted to the FDA at this data cut, although this had not been explicitly requested. A final analysis was originally planned for the point at which approx. 118 primary outcome events had occurred (after approx. 40 months). This prespecified final analysis was not carried out, as the study was terminated prematurely by an external data monitoring committee due to the results of the interim analysis.

AE: adverse event; FDA: US Food and Drug Administration; n: subpopulation analysed by the company; N: number of randomized (included) patients; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; REVEAL: Registry to Evaluate Early and Long-Term PAH Disease Management; WHO: World Health Organisation; WU: Wood units

Table 6: Characteristics of the intervention – RCT, direct comparison: sotatercept vs. placebo

Study	Intervention	Comparison
ZENITH	Sotatercept SC ▪ starting dose: 0.3 mg/kg body weight ▪ target dose from Week 3: 0.7 mg/kg body weight every 3 weeks	▫ Placebo SC every 3 weeks
	Dose modification: ▪ dose delays or dose reductions to 0.3 mg/kg or discontinuation if the Hb level increases by > 2 g/dL from the previous cycle, low platelet count (< 50 000/mm³) or due to AEs (e.g. telangiectasia)	
	Prior and concomitant treatment ▪ <u>required</u> ▪ stable doses of background PAH [a] for ≥ 30 days prior to screening allowed ▪ drug treatment of chronic diseases with a stable dosage[b] disallowed ▪ coronary artery bypass surgery ≤ 6 months before screening	

a. Maximum tolerated dose of a dual or triple combination therapy, as determined by the investigator, consisting of at least two drugs from different drug classes, choosing from ERA, PDE5I, sGC stimulators, PCA and/or PRA. PAH background therapy had to be kept stable throughout the study, although a dose adjustment of up to 10% was permitted for parenteral prostacyclines.
b. In cases of immediate medical need, the dose could be adjusted and new medication could be initiated.

ERA: endothelin receptor antagonists; Hb: haemoglobin; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogues; PDE5I: phosphodiesterase type 5 inhibitors; PRA: prostacyclin receptor antagonists; RCT: randomized controlled trial; SC: subcutaneous; sGC: soluble guanylate cyclase

The ZENITH study is a completed, multicentre, double-blind RCT comparing sotatercept with placebo, each in addition to background PAH therapy, in adults with PAH in WHO functional class III or IV and at high risk of mortality.

Adult patients with PAH (WHO group 1), in the subtypes of idiopathic PAH, heritable PAH, drug/toxin-induced PAH, PAH associated with connective tissue disease, or PAH associated with simple, congenital systemic-to-pulmonary shunts, confirmed by right heart catheterization were enrolled in the study. Patients had to have symptomatic PAH in WHO functional class III or IV, a REVEAL Lite 2 risk score of ≥ 9, and they had to be clinically stable. In addition, the patients had to have a pulmonary vascular resistance of ≥ 5 Wood units (WU) and a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure of ≤ 15 mmHg according to right heart catheterization during screening. To be eligible for inclusion in the study, patients had to have been receiving the maximum tolerated dose of background PAH therapy, as determined by the investigator, at a stable dose for ≥ 30 days prior to screening and continue this therapy throughout the study; for parenteral prostacyclines, a dose adjustment of up to 10% was permitted.

A total of 173 patients were included in the study and randomly assigned in a 1:1 ratio to either sotatercept (N = 86) or placebo (N = 87); one patient in the placebo arm was randomized in error and was immediately excluded from the study prior to administration of the study medication; this patient was not considered in the analysis populations. Randomisation was stratified according to the REVEAL Lite 2.0 risk score (9 to 10 vs. ≥ 11) and PAH subtype (associated with connective tissue disease vs. not associated with connective tissue disease). A total of 44 patients were classified as WHO functional class IV in accordance with the therapeutic indication relevant to this dossier assessment (sotatercept arm: n = 20, placebo arm: n = 24).

Treatment with sotatercept was largely in compliance with the SmPC [13]. The specified background PAH therapy in the ZENITH study was a dual or triple combination therapy, as determined by the investigator, consisting of at least two drugs from different drug classes, choosing from ERA, PDE5I, sGC stimulators, PRA and/or PCA. Patients were required to have been receiving the maximum tolerated dose, as determined by the investigator, at a stable dose for ≥ 30 days prior to screening and were to continue this dose throughout the study, with a dose adjustment of up to 10% being permitted for parenteral prostacyclins. Drug treatment of chronic diseases other than PAH was permitted at a stable dose, regardless of the drugs used.

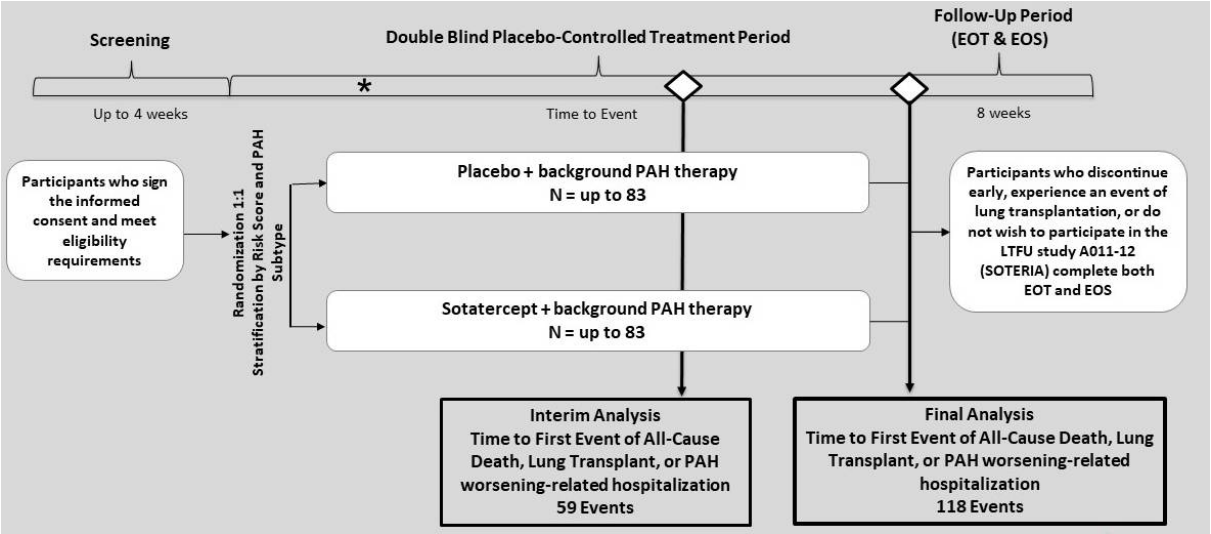
The primary outcome of the ZENITH study was the time to occurrence of the first event in a composite outcome comprising hospitalization for ≥ 24 hours due to worsening PAH, lung transplantation or death from any cause. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

For a characterization of the study population in the ZENITH study, see Table 8 of the full dossier assessment (subpopulation with WHO functional class IV) and Table 9 of the full dossier assessment (total population) in I Appendix B.

Data cuts and observation period

No fixed duration was specified for the ZENITH study; instead, data cuts were planned depending on the number of events occurring in the primary outcome (see Figure 1). Following completion of the double-blind, placebo-controlled treatment phase (from Amendment 2 to the study protocol of 29 June 2023, also following hospitalization for ≥ 24 hours due to worsening PAH), patients in both study arms could transfer to the SOTERIA extension study [14] and receive treatment with sotatercept as part of this study. According to the information provided in Module 4A, one patient from the sotatercept arm and seven patients from the placebo arm had transitioned into the SOTERIA extension study by the time of the first data cut on 26 July 2024; information on at the second data cut of 6 June 2025 is not available. Patients who discontinued treatment prematurely or who underwent a lung

transplant and were therefore unable to switch to the SOTERIA extension study, as well as patients who did not switch to the SOTERIA extension study for other reasons, were followed up for approx. 8 weeks after the end of treatment as part of the ZENITH study, with mortality data also being recorded beyond the final study visit up to the data cut.



EoT: end of treatment; EoS: end of study; LTFU: long-term follow-up; PAH: pulmonary arterial hypertension.
∗ Assessments will be collected at the 6-month visit (Visit 9) for secondary endpoint analysis.

Figure 1: Design of the ZENITH study [7]

Two data cuts were available for the ZENITH study:

- First data cut on 26 July 2024 (prespecified interim analysis, planned for the point in time at which approx. 59 primary outcome events had occurred and a median follow-up period of at least 6 months had elapsed)
- Second data cut on 6 June 2025 (non-prespecified final analysis at the end of the study; the last visit took place on 18 February 2025, with the final data cut and simultaneous database lock on 6 June 2025)

A final analysis was originally planned for the point at which approx. 118 primary outcome events had occurred (after approx. 40 months). This prespecified final analysis was not carried out, as the study was terminated prematurely by an external data monitoring committee due to the results of the interim analysis. At this point in time, the median follow-up duration for the total population in the ZENITH study was 10.6 months in the sotatercept arm and 7.1 months in the placebo arm, with 20.9% of patients in the sotatercept arm and 40.7% in the placebo arm having a follow-up duration of less than 6 months. The final analysis carried out at the end of the study was conducted in accordance with the company in order to submit safety data to the US Food and Drug Administration (FDA); however, these data had not been explicitly requested. At that point in time, the median observation period in the ZENITH study

for the total population was 14.6 months in the sotatercept arm and 8.9 months in the placebo arm, with 8.1% of patients in the sotatercept arm and 29.1% in the placebo arm having a follow-up duration of less than 6 months. In Module 4A, the company states that the median observation period for the outcome overall survival and the primary study outcome was 54 weeks (12.4 months) in the intervention arm and 32 weeks (7.4 months) in the control arm (for the subpopulation with WHO functional class IV). In doing so, it does neither specify the data cut it refers to, nor does it mention the proportion of patients who were followed-up for less than 6 months.

Module 4A contains discrepant information on the time point of the second data cut. In particular, the headings of the tables on the second data cut (in Appendix 4-G to Module 4A) in mention 18 February 2025 as the date of the database cut, whilst the footnote in the same tables states 'Database Cutoff Date: 06JUN2025'. 18 February 2025 is the date of the last visit, whilst, according to the clinical study report, the second data cut with simultaneous final database lock, took place on 6 June 2025. In the ZENITH study, mortality data were recorded beyond the final visit up to the data cut, meaning that further data could still be added after 18 February 2025.

In its dossier, the company uses the results of the first data cut of 26 July 2024 (interim analysis) and also presents the results of the second data cut of 6 June 2025 as supplementary information (final analysis at the end of the study).

I 3.2 Assessment of the evidence presented by the company

In this situation involving a high mortality risk, it can be assumed that patient-relevant events can be meaningfully recorded even over an observation period shorter than 24 weeks. Despite its event-driven design and the resulting observation period of less than 24 weeks for a relevant proportion of patients, the RCT ZENITH is therefore potentially relevant for the benefit assessment. However, due to a lack of information on the implementation of that therapy, the analyses of the ZENITH study submitted by company are not suitable for drawing conclusions regarding the added benefit of sotatercept compared with the ACT. This is further explained below.

I 3.2.1 Missing data on the implementation of the ACT

For the present therapeutic indication, the G-BA determined a triple therapy with epoprostenol + ERA + PDE5I as the ACT. The comparator therapy in the ZENITH study was placebo under the continuation of an existing dual or triple combination therapy with at least two drugs from different drug classes, choosing from ERA, PDE5I, sGC stimulators, PCA and/or PRA. Whilst this includes all drugs specified in the G-BA's ACT, it does not mandate a triple therapy with epoprostenol + ERA + PDE5I for all patients, but also permits dual therapies and

other drug classes (sGC stimulators, PRA and PCA other than epoprostenol). The comparator therapy in the ZENITH study is therefore wider than the G-BA's ACT.

Almost all patients in the ZENITH study had an intermediate-high or high risk of mortality according to the COMPERA 2.0 4-strata risk score (see Table 9 in I Appendix B). According to the ESC/ERS guidelines, additional parenteral PCA therapy (i.e. a triple therapy of parenteral PCA + ERA + PDE5I) and evaluation for lung transplant should be considered for patients in this therapeutic indication who present an intermediate-high or high risk of mortality under dual therapy with ERA + PDE5I, and who have no cardiopulmonary comorbidities [5]. A simple continuation of a dual therapy or of a therapy without parenteral PCA is therefore not compliant with the guideline's recommendation for these patients.

The company's dossier does not provide any information on how many patients in the ZENITH study received triple therapy with epoprostenol (or another parenteral PCA). In the subpopulation with WHO functional class IV, around 70% of patients in both study arms received triple therapy, and around 55% of patients in both study arms received intravenous PCA therapy, which potentially includes epoprostenol (see Table 8 in I Appendix B). However, no information is available on the drugs or drug combinations used in each case. At least 45% of patients in the subpopulation with WHO functional class IV did not receive intravenous PCA therapy and thus no epoprostenol. The ACT specified by the G-BA was therefore not implemented for a relevant proportion of patients.

In accordance with the G-BA's notes on the ACT, the unsuitability of epoprostenol must be documented and discussed in the dossier for study participants receiving combination therapy without epoprostenol. This was not done. The case report form asked about the reasons for not using triple therapy (regardless of the drugs used). Reasons given could include concerns regarding tolerability, lack of availability or reimbursement, or refusal by the patient. However, the results of this enquiry are not provided in the company's dossier, neither for the subpopulation with WHO functional class IV nor for the total population. The dossier contains no information indicating that the reasons for not using epoprostenol or parenteral PCA therapy in general were recorded or documented. Data on cardiopulmonary comorbidities are available for the total population; these may provide clues as to possible reasons for the non-use of epoprostenol (see Table 9 in I Appendix B.2). Relevant data for the subpopulation of patients in WHO functional class IV are not available. Overall, the company's dossier does not indicate how many patients who did not receive triple therapy with epoprostenol (or another parenteral PCA) would not have been eligible for it.

Irrespective of this, it should be pointed out with regard to the G-BA's notes on a possible individualized concomitant medication (oxygen therapy, diuretics, anticoagulants) that any concomitant medication for chronic conditions, including PAH, should be kept stable throughout the study. Only in cases of immediate medical need, the dose could be adjusted

and new medication could be initiated. The investigator should consult the Medical Monitor to clarify what constitutes a stable dosage or a chronic condition. Individualized concomitant medication was thus possible, although this requirement may have made this more difficult. With regard to the G-BA's note on non-drug interventions as part of the background therapy in both study arms, it should be noted that no non-drug interventions were offered as part of the study. The ZENITH study investigated the participation in an exercise programme on cardiopulmonary rehabilitation, as well as the reasons for any non-participation. However, the dossier does not contain any relevant information for the subpopulation with WHO functional class IV. In the total population, only 6 patients in the sotatercept arm (7%) and 5 patients in the comparator arm (6%) underwent an exercise programme for cardiopulmonary rehabilitation. According to the investigator`s assessment, such an exercise programme was not recommended for 48 (56%) versus 54 (63%) of the patients. In contrast, for 21 (24%) versus 24 (28%) of the patients, the reason given for non-participation was lack of reimbursement or local availability.

In summary, both in the total population and in the subpopulation of patients with WHO functional class IV, treatment in the comparator arm of the ZENITH study did not correspond to the ACT for a relevant proportion of patients. This means that no suitable data were available for the comparison of sotatercept with the G-BA's comparator therapy.

I 3.2.2 Further limitations of the analyses presented in the ZENITH study

In addition to the missing information regarding the ACT described in Section I 3.2.1, there are further limitations of the analyses presented, which are described below.

Unclear relevance of the data cut at the end of the study

As described in Section I 3.1, a second, non-prespecified data cut was performed at the end of the ZENITH study. The analyses on this data cut (final analysis at the end of the study) are potentially suitable for the benefit assessment, despite the lack of prespecification, as the data cut was performed at the end of the study and thus at a non-arbitrary point in time. The company has not explained that this data cut had not yielded any relevant information gain compared with the first data cut (interim analysis), the results of which it uses in its dossier on the benefit assessment. The results of the final analysis are not as complete as those of the interim analysis. In particular, the results of the sensitivity analysis on overall survival (including deaths following lung transplant and following transition to the SOTERIA extension study) are missing, both for the subpopulation with WHO functional class IV and for the total population, as well as subgroup analyses for all presented outcomes and response rates of the questionnaires used.

Uncertainties regarding the analyses on overall survival

Sensitivity analyses and transition to the SOTERIA extension study

In the ZENITH study, overall survival was defined as death from any cause up to the time point of the data cut. The study documents provide various analyses on overall survival:

- Main analysis (presented as a sensitivity analysis in M 4A): death from any cause up to the data cut, excluding events that occurred following lung transplantation or transition to the SOTERIA extension study.
- Sensitivity analysis (presented as the primary analysis in M 4A): death from any cause up to the data cut, including events that occurred following lung transplant or transition to the SOTERIA extension study.

The main analysis, which excludes events occurring after lung transplant or transition to the SOTERIA extension study, was prespecified. Following the first data cut of 26 July 2024, the sensitivity analysis described above, which includes events following lung transplant or transition to the SOTERIA extension study, was defined with version 2 of the statistical analysis plan on 30 September 2024. As already described in the previous section, the company did not present any results from the sensitivity analysis for the second data cut of the ZENITH study, although it used them as the primary analysis for deriving the added benefit for the first data cut in Module 4A. The company justified this on the grounds that the results of the second data cut were not used to derive the added benefit, as this had not been prespecified.

Analyses of overall survival, including all deaths (even following intercurrent events such as a lung transplant or hospitalization), were preferred. The conducted sensitivity analysis considers deaths following lung transplant and following hospitalization; it should be noted, however, that when patients from the comparator arm of the ZENITH study transitioned to the SOTERIA extension study, treatment was changed from placebo to sotatercept. To interpret the sensitivity analysis, it is necessary to understand the patient flow in detail. Module 4A merely states that, at the time of the first data cut, one patient from the sotatercept arm and seven patients from the placebo arm in the ZENITH study subpopulation with WHO functional class IV, had transitioned to the SOTERIA extension study. For the second data cut, no corresponding data are available either for the subpopulation of the ZENITH study with WHO functional class IV or for the total population. It is not clear from the information on observation periods for overall survival in Module 4A whether these take into account the follow-up carried out as part of the SOTERIA study. Unlike at the time of the first data cut, when transitions to SOTERIA were only permitted following hospitalization of ≥ 24 hours due to worsening PAH, data on the reason for the transition are required at the second data cut, as the sponsor’s termination of the study entails a non-informative reason for a transition.

Analysis of the total population

In Module 4A, the company presents the results of the sensitivity analysis for overall survival (i.e. including deaths following lung transplant or transition to the SOTERIA extension study) for the total population of the ZENITH study at the first data cut and, based on these results and by a transfer to the population of patients with WHO functional class IV, derives an indication of an non-quantifiable added benefit. It justifies this approach on the grounds that, in the subpopulation with WHO functional class IV, there are simply too few patients for the demonstration of a statistically significant effect. For the total population, it does not provide any of the data described in the previous section regarding transitions to the SOTERIA extension study. The observation period for this analysis is also unclear. Related to the analyses of the total population of the ZENITH study used by the company for overall survival, it should also be noted that the company's dossier contains no information or analyses as to the extent to which the WHO functional class (III vs. IV) is a relevant effect modifier for overall survival in the context of this comparison. The company justified the transfer of the results of the total population to the subpopulation with WHO functional class IV solely on the grounds that the mortality risk among more severely ill patients in WHO functional class III is comparable to that of patients in WHO functional class IV.

Uncertainties and missing data regarding subgroup analyses

In Module 4A, the company states that the characteristic region was prespecified. However, there is no relevant information in the study protocol or the statistical analysis plan. In Module 4A, the company therefore conducts post-hoc subgroup analyses based on the regions WHO Stratum A and the rest of the world , whereby the latter region comprises Mexico alone and includes so few patients (1 patient in the sotatercept arm and 2 patients in the placebo arm) that analyses for the characteristic region are not calculable. In Module 4A, the company also classifies regions into WHO Stratum A and rest of the world when presenting patient characteristics. Deviating from this, the clinical study report distinguishes between the regions Europe (51% of the total population), North America (47%) and Asia/Pacific (2%) in terms of patient characteristics. If the regional distribution was comparable within the subpopulation with WHO functional class IV, subgroup analyses for the characteristic region could potentially be calculated. The company does not explain why its classification of the regions in Module 4A differs from the clinical study report. Selective reporting cannot be excluded.

Irrespective of this, Module 4A does not include subgroup analyses for all submitted operationalizations of the presented outcomes, even though these could potentially be calculated. In particular, subgroup analyses are missing for the analyses on overall survival in the total population used by the company, for several operationalizations of the 6-minute walk test (6MWT) in the subpopulation with WHO functional class IV, and for all outcomes at the second data cut.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of sotatercept in combination with other PAH therapies over the ACT in adults with PAH with WHO functional class IV. There is no hint of an added benefit of sotatercept in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of sotatercept in comparison with the ACT is summarised in Table 7.

Table 7: Sotatercept – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with WHO functional class IV PAH	Epoprostenol in combination with ERAs (ambrisentan, bosentan, macitentan) and PDE5is (sildenafil, tadalafil)[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. No drugs other than the PCA epoprostenol are approved for the treatment of patients with PAH with WHO functional class IV. According to the G-BA, the off-label use of a combination therapy with an ERA and PDE5I, in addition to the approved epoprostenol, is regarded as the therapy standard in the therapeutic indication under assessment and is generally to be preferred to monotherapy with drugs containing the active substance epoprostenol that have previously been approved for the therapeutic indication (Section 6(2), sentence 3, point 2 of the AM-NutzenV).
c. Further comments from the G-BA:

- The guideline recommends a combination therapy comprising ERA, PDE5I and PCA for the treatment of patients with PAH in WHO functional class IV. According to feedback from clinical experts, this treatment regimen currently represents the therapy standard for the majority of patients in the considered indication. Where study participants are receiving combination therapy without epoprostenol, the fact that these individuals are not suitable for treatment with epoprostenol must be documented and discussed in the dossier of the benefit assessment.
- It is assumed that combination therapies are generally used in this therapeutic indication. Furthermore, it is assumed that all patients in both study arms will have access to the continuation of the treatment options approved for less serious WHO functional classes, or that these treatment options will be initiated in case of a corresponding therapeutic indication.
- It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
- In principle, a lung transplant or a heart-lung transplant is a treatment option for patients with WHO functional class IV. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication.
- There are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic measures in the sense of the Remedies Directive (physical therapy, e.g. physiotherapy, if indicated, should be made available to patients in both arms of the study in addition to drug therapy.

ERA: endothelin receptor antagonist; G-BA: Federal Joint Committee; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogues; PDE5I: phosphodiesterase-5 inhibitors; WHO: World Health Organization

The assessment described above deviates from that of the company, which derives an indication of considerable added benefit for adults with WHO functional class IV PAH who cannot receive treatment escalation with other PAH therapies.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 8.0 [online]. 2025 [Accessed: 07.01.2026]. URL: https://doi.org/10.60584/Allgemeine-Methoden_V8.0.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Niederschrift zum Beratungsgespräch gemäß § 8 Abs. 1 AM-NutzenV. Beratungsanforderung 2025-B-098. Sotatercept zur Behandlung der Pulmonal Arteriellen Hypertonie (PAH) bei erwachsenen Patient:innen mit WHO-FK IV [unpublished]. 2025.

4. Gemeinsamer Bundesausschuss. Niederschrift zum Beratungsgespräch gemäß § 8 Abs. 1 AM-NutzenV. Beratungsanforderung 2025-B-262. Sotatercept zur Behandlung der Pulmonal Arteriellen Hypertonie (PAH) bei erwachsenen Patient:innen mit WHO-FK IV [unpublished]. 2025.

5. Humbert M, Kovacs G, Hoeper MM et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2022; 61(1). https://doi.org/10.1183/13993003.00879-2022.

6. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) und Anlage XIIa – Kombinationen von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Sotatercept (Pulmonale arterielle Hypertonie) [online]. 2025. URL: https://www.g-ba.de/downloads/40-268-11277/2025-03-06_AM-RL-XII-XIIa_Sotatercept_D-1104_TrG.pdf.

7. Merck, Sharp & Dohme. Clinical Study Report: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality (26-FEB-2025) [unpublished]. 2025.

8. Merck, Sharp & Dohme. Clinical Study Report: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality (10-JUL-2025) [unpublished]. 2025.

9. Acceleron Pharma. A Study of Sotatercept in Participants With PAH WHO FC III or FC IV at High Risk of Mortality (MK-7962-006/ZENITH) (ZENITH) [online]. 2026 [Accessed: 18.03.2026]. URL: https://clinicaltrials.gov/study/NCT04896008.

10. Acceleron Pharma. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) W [online]. [Accessed: 18.03.2026]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-001498-21.

11. Acceleron Pharma. A Phase 3, Randomized, Double-Blind, Placebo_Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality [online]. 2024 [Accessed: 18.03.2026]. URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-509140-10-00.

12. Humbert M, McLaughlin VV, Badesch DB et al. Sotatercept in Patients with Pulmonary Arterial Hypertension at High Risk for Death. N Engl J Med 2025; 392(20): 1987-2000. https://doi.org/10.1056/NEJMoa2415160.

13. MSD Sharp & Dohme. Winrevair 45 mg/- 60 mg Pulver und Lösungsmittel zur Herstellung einer Injektionslösung [online]. 01.2026 [Accessed: 17.02.2026]. URL: https://www.fachinfo.de/.

14. Acceleron Pharma. A Long-term Follow-up Study of Sotatercept for PAH Treatment (MK-7962-004/A011-12) (SOTERIA) [online]. 2024 [Accessed: 21.11.2024]. URL: https://clinicaltrials.gov/study/NCT04796337.

The full report (German version) is published at https://www.iqwig.de/en/projects/a26-12.html.