Sotatercept
(pulmonary arterial hypertension)

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

EXTRACT

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IQWiG thanks the medical and scientific advisor for his 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 was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
6MWT	6-minute walking test
ACT	appropriate comparator therapy
ERS	European Respiratory Society
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NT-proBNP	N-terminal pro-brain natriuretic peptide
PAH	pulmonary arterial hypertension
PDE-5	phosphodiesterase type 5
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
WHO	World Health Organization
WU	Wood unit

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 17 September 2024.

Research question

The aim of this report is to assess the added benefit of sotatercept in combination with other pulmonary arterial hypertension (PAH) therapies to improve exercise capacity in adult patients with PAH with World Health Organization (WHO) functional class II to III, in comparison with the appropriate comparator therapy (ACT).

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of sotatercept

Therapeutic indication	**ACT[a]**
Treatment of PAH in adult patients with WHO functional class II to III, to improve exercise capacity[b, c]	Individualized therapy[d, e, f] taking into account prior therapies and health status, with a choice of the following therapies: ▪ endothelin receptor antagonists (ambrisentan, bosentan, macitentan) ▪ phosphodiesterase type 5 inhibitors (sildenafil, tadalafil) ▪ prostacyclin analogues (iloprost)[g] ▪ selective prostacyclin receptor agonists (selexipag) ▪ soluble guanylate cyclase stimulator (riociguat)

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients included in the study are not eligible for a lung transplant or a heart-lung transplant.
c. According to the G-BA, it can be inferred from the guideline recommendations that treatment with calcium antagonists alone is indicated if the patients have a positive vasoreactivity test. However, targeted PAH therapy (e.g. with endothelin receptor antagonists, phosphodiesterase type 5 inhibitors) is recommended for patients with a negative vasoreactivity test and for vasoreactive patients who no longer respond to treatment with calcium antagonists alone. Therefore, it is assumed that the patients included in the study are not eligible for treatment with calcium channel blockers alone.
d. For the implementation of individualized therapy in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). Usually, combination therapies are used in the present therapeutic indication. If monotherapy is indicated in the comparator arm, this must be justified in the dossier. Continuation of an inadequate therapy does not constitute an implementation of the ACT. The sole dose optimization of a monotherapy or a change of drugs within a monotherapy does not correspond to the ACT.
e. According to the G-BA, there are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic measures can be indicated in the sense of both the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) and a targeted training therapy to improve performance (e.g. after a surgical treatment). Only patients without notable limitations of resilience are eligible for the specific training therapy to increase performance, while physiotherapeutic measures in the sense of the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) may be suitable for all patients. Physiotherapeutic measures, if indicated, should be made available to patients in both arms of the study in addition to drug therapy.
f. It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
g. Although the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally only, are approved for WHO/NYHA class III, it is assumed in accordance with the G-BA that the continuous, subcutaneous, or intravenous use of prostacyclin analogues usually applies to advanced disease only, so that this option is not considered an ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; WHO: World Health Organization

The company followed the G-BA's ACT, but also considered the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally, as part of the ACT.

The present benefit assessment is conducted in comparison with the ACT specified by the G-BA. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for deriving any added benefit.

Results

The check of completeness of the study pool identified the RCT STELLAR comparing sotatercept with placebo, each in addition to background PAH therapy, as potentially relevant study. Based on the information available, it is unclear whether the STELLAR study contains a relevant subpopulation for the present benefit assessment. The company used the total population of this study to assess the added benefit of sotatercept.

Evidence provided by the company

The STELLAR study is a completed, multicentre, double-blind RCT on treatment with sotatercept. The study investigated the comparison of sotatercept with placebo, each in addition to background PAH therapy.

Adult patients with PAH (WHO group 1) confirmed by right heart catheterization were enrolled. Patients had to have symptomatic PAH classified as WHO functional class II or III and be able to walk between ≥ 150 m and ≤ 500 m in the 6-minute walking test (6MWT). 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.

The study included a total of 323 patients who were randomly allocated in a 1:1 ratio to sotatercept (N = 163) or placebo (N = 160).

Treatment in the STELLAR study was divided into a primary treatment phase and a long-term treatment phase. The duration of the primary treatment phase was 24 weeks. After completion of the primary treatment phase, patients continued their treatment according to randomization for up to 72 weeks, with blinding being maintained. After the last included patient had completed the primary treatment phase, the study was unblinded. Subsequently, all patients could receive sotatercept in the SOTERIA extension study.

Treatment with sotatercept was largely in compliance with the Summary of Product Characteristics (SPC). For ≥ 90 days prior to screening, patients enrolled in the study had to be on stable doses of background PAH therapy, consisting of monotherapy or combination therapy with endothelin receptor antagonists, PDE5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues and/or selective prostacyclin receptor agonists. The patient-specific dose goal for each PAH therapy had to be already achieved at study entry. Background therapy had to remain stable throughout the study.

The primary outcome of the STELLAR study was the change in 6MWT walking distance at Week 24 from baseline. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Assessment of the evidence presented by the company

Appropriate comparator therapy not implemented in the STELLAR study

For the present therapeutic indication, the G-BA defined individualized therapy with a choice of the several drugs as ACT. The G-BA further specified the implementation of individualized therapy in its additional notes. According to these notes, it is assumed, among other things, that the continuous, subcutaneous, or intravenous use of prostacyclin analogues usually applies to advanced disease only, so that the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally, are not considered an ACT. Around 40% of patients in both study arms of the STELLAR study received treatment with parenteral prostacyclin analogues, however. The ACT defined by the G-BA was therefore not implemented for a relevant proportion of patients.

Furthermore, irrespective of therapy with parenteral prostacyclin analogues, there are uncertainties as to whether the individualized therapy was adequately implemented in the STELLAR study. In the STELLAR study, sotatercept was compared with placebo, with patients in both study arms receiving background PAH therapy. Background therapy had to be stable for ≥ 90 days prior to screening and had to remain stable throughout the study. Hence, there was no treatment optimization at any time during the study.

Furthermore, no information is available on the respective dosage of the drugs used in background therapy. It is not possible to check the approval-compliant dosage of the drugs on the basis of the information available. It is also questionable whether the patients in the STELLAR study had sufficient access to non-drug physiotherapeutic measures.

In summary, the analyses presented by the company on the total population of the STELLAR study are not suitable for the benefit assessment due to the lack of implementation of the ACT. It is unclear whether the study population of the STELLAR study includes a relevant subpopulation for which the ACT defined by the G-BA was adequately implemented.

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.

[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 less benefit). For further details see [1,2].

Table 3: Sotatercept – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Treatment of PAH in adult patients with WHO functional class II to III, to improve exercise capacity[b, c]	Individualized therapy[d, e, f] taking into account prior therapies and health status, with a choice of the following therapies: ▪ endothelin receptor antagonists (ambrisentan, bosentan, macitentan) ▪ phosphodiesterase type 5 inhibitors (sildenafil, tadalafil) ▪ prostacyclin analogues (iloprost)[g] ▪ selective prostacyclin receptor agonists (selexipag) ▪ soluble guanylate cyclase stimulator (riociguat)	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients included in the study are not eligible for a lung transplant or a heart-lung transplant.
c. According to the G-BA, it can be inferred from the guideline recommendations that treatment with calcium antagonists alone is indicated if the patients have a positive vasoreactivity test. However, targeted PAH therapy (e.g. with endothelin receptor antagonists, phosphodiesterase type 5 inhibitors) is recommended for patients with a negative vasoreactivity test and for vasoreactive patients who no longer respond to treatment with calcium antagonists alone. Therefore, it is assumed that the patients included in the study are not eligible for treatment with calcium channel blockers alone.
d. For the implementation of individualized therapy in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). Usually, combination therapies are used in the present therapeutic indication. If monotherapy is indicated in the comparator arm, this must be justified in the dossier. Continuation of an inadequate therapy does not constitute an implementation of the ACT. The sole dose optimization of a monotherapy or a change of drugs within a monotherapy does not correspond to the ACT.
e. According to the G-BA, there are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic measures can be indicated in the sense of both the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) and a targeted training therapy to improve performance (e.g. after a surgical treatment). Only patients without notable limitations of resilience are eligible for the specific training therapy to increase performance, while physiotherapeutic measures in the sense of the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) may be suitable for all patients. Physiotherapeutic measures, if indicated, should be made available to patients in both arms of the study in addition to drug therapy.
f. It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
g. Although the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally only, are approved for WHO/NYHA class III, it is assumed in accordance with the G-BA that the continuous, subcutaneous, or intravenous use of prostacyclin analogues usually applies to advanced disease only, so that this option is not considered an ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; WHO: World Health Organization

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 to improve exercise capacity in adult patients with PAH with WHO functional class II to III, in comparison with the ACT.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of sotatercept

Therapeutic indication	**ACT[a]**
Treatment of PAH in adult patients with WHO functional class II to III, to improve exercise capacity[b, c]	Individualized therapy[d, e, f] taking into account prior therapies and health status, with a choice of the following therapies: ▪ endothelin receptor antagonists (ambrisentan, bosentan, macitentan) ▪ phosphodiesterase type 5 inhibitors (sildenafil, tadalafil) ▪ prostacyclin analogues (iloprost)[g] ▪ selective prostacyclin receptor agonists (selexipag) ▪ soluble guanylate cyclase stimulator (riociguat)

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients included in the study are not eligible for a lung transplant or a heart-lung transplant.
c. According to the G-BA, it can be inferred from the guideline recommendations that treatment with calcium antagonists alone is indicated if the patients have a positive vasoreactivity test. However, targeted PAH therapy (e.g. with endothelin receptor antagonists, phosphodiesterase type 5 inhibitors) is recommended for patients with a negative vasoreactivity test and for vasoreactive patients who no longer respond to treatment with calcium antagonists alone. Therefore, it is assumed that the patients included in the study are not eligible for treatment with calcium channel blockers alone.
d. For the implementation of individualized therapy in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). Usually, combination therapies are used in the present therapeutic indication. If monotherapy is indicated in the comparator arm, this must be justified in the dossier. Continuation of an inadequate therapy does not constitute an implementation of the ACT. The sole dose optimization of a monotherapy or a change of drugs within a monotherapy does not correspond to the ACT.
e. According to the G-BA, there are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic measures can be indicated in the sense of both the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) and a targeted training therapy to improve performance (e.g. after a surgical treatment). Only patients without notable limitations of resilience are eligible for the specific training therapy to increase performance, while physiotherapeutic measures in the sense of the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) may be suitable for all patients. Physiotherapeutic measures, if indicated, should be made available to patients in both arms of the study in addition to drug therapy.
f. It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
g. Although the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally only, are approved for WHO/NYHA class III, it is assumed in accordance with the G-BA that the continuous, subcutaneous, or intravenous use of prostacyclin analogues usually applies to advanced disease only, so that this option is not considered an ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; WHO: World Health Organization

The company followed the G-BA's ACT, but also considered the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally, as part of the ACT. It

justified this by stating that both treprostinil and epoprostenol are approved for the treatment of PAH in patients with WHO functional class III and are recommended in the current guideline of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) [3] for patients who are not satisfactorily treated with a combination of an endothelin receptor antagonist and a phosphodiesterase type 5 (PDE-5) inhibitor and who are at intermediate-high or high risk. According to the company, the guideline recommendations also apply to patients of WHO functional class III with a corresponding risk profile. According to the company's argumentation, it should also be taken into account that adding prostacyclin analogues can improve patients' WHO functional class, which means that prostacyclin analogues become a permanent part of the medication plan (see Section I 3.2).

The present benefit assessment is conducted in comparison with the ACT specified by the G-BA. The assessment is 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 are used for deriving any added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on sotatercept (status: 7 August 2024)
- bibliographical literature search on sotatercept (last search on 9 July 2024)
- search in trial registries/trial results databases for studies on sotatercept (last search on 9 July 2024)
- search on the G-BA website for sotatercept (last search on 9 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on sotatercept (last search on 24 September 2024); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool identified the RCT STELLAR [4-7] comparing sotatercept with placebo, each in addition to background PAH therapy, as potentially relevant study. Based on the information available, it is unclear whether the STELLAR study contains a relevant subpopulation for the present benefit assessment. The company used the total population of this study to assess the added benefit of sotatercept.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of sotatercept in comparison with the ACT. Below, the STELLAR 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 the STELLAR study

Table 5 and Table 6 describe the STELLAR study presented by the company for the benefit assessment. For a characterization of the study population of the STELLAR study, see Table 8 in I Appendix B of the full dossier 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 randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
STELLAR	RCT, double-blind, parallel	Adults (≥ 18 years) with symptomatic PAH (WHO group I)[b, c] ▪ WHO functional class II or III ▪ 6MWT ≥ 150 m and ≤ 500 m at screening	Sotatercept (N = 163) Placebo (N = 160)	Screening: up to 4 weeks Treatment: ▪ DBPC treatment phase: 24 weeks ▪ LTDB treatment phase: up to 72 weeks[d] Follow-up[e]: 8 weeks	91 study centres in Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, Korea, Mexico, Netherlands, New Zealand, Poland, Serbia, Spain, Sweden, Switzerland, United Kingdom, United States 1/2021–12/2022 Data cut-offs ▪ 26 August 2022[f] (basis for approval) ▪ 6 December 2022[g] (final analysis)	Primary: Change in 6MWT at Week 24 Secondary: 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 randomized 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's 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. After completion of the 24-week DBPC treatment phase, patients continued blinded treatment with their respective study medication in the LTDB treatment phase until the last included patient had completed the DBPC treatment phase, and the study was unblinded. After completion of the randomized controlled treatment, patients could transition into the SOTERIA extension study.
e. Follow-up was conducted in patients who discontinued the study early for reasons other than clinical deterioration or who did not transition into the SOTERIA extension study.
f. After all patients had completed the 24-week DBPC treatment phase; last visit after 24 weeks of the last patient: 26 August 2022.
g. Date of the last visit of the last patient.

6MWT: 6-minute walking test; AE: adverse event; DBPC: double-blind placebo-controlled; LTDB: long-term double-blind; N: number of randomized patients; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; WHO: World Health Organization

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

Study	Intervention	Comparison
STELLAR	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 adjustment: ▪ Dose delays or dose reductions to 0.3 mg/kg 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 ≥ 90 days prior to screening <u>Allowed</u> ▪ treatment of chronic conditions throughout the study ▪ stable doses of diuretics[b] for ≥ 90 days prior to screening <u>Disallowed</u> ▪ initiation of an exercise programme for cardiopulmonary rehabilitation ≤ 90 days prior to screening or during the study[c] ▪ intravenous inotropes (e.g. dobutamine, dopamine, norepinephrine, vasopressin) ≤ 30 days prior to screening	

a. Monotherapy or combination therapy with endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues and/or selective prostacyclin receptor agonists. Background PAH therapy had to remain stable throughout the study.
b. Addition of a diuretic that had not been given before study start or switching of an oral diuretic to parenteral administration was not allowed throughout the study. Dose adjustments in oral diuretics that had already been given before study start were allowed.
c. The continuation of an ongoing exercise programme for cardiopulmonary rehabilitation during the study was permitted.

AE: adverse event; Hb: haemoglobin; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; SC: subcutaneous

The STELLAR study is a completed, multicentre, double-blind RCT on treatment with sotatercept. The study investigated the comparison of sotatercept with placebo, each in addition to background PAH therapy.

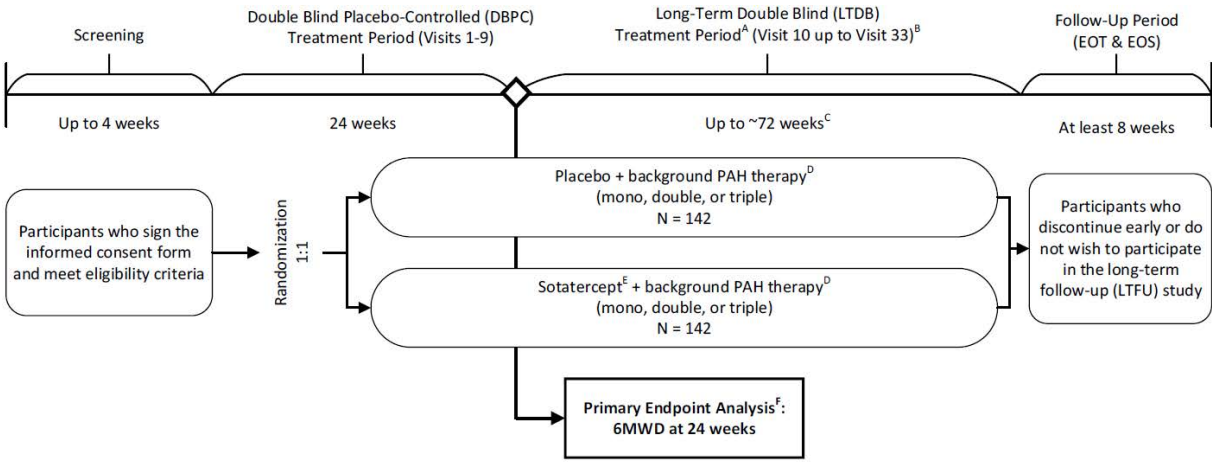
Adult patients with PAH (WHO group 1), in the subtypes of idiopathic PAH, heritable PAH, drug/toxin-induced PAH, PAH associated with connective tissue disease, or PAH associated with simple, congenital systemic-to-pulmonary shunts, confirmed by right heart catheterization were enrolled. Patients had to have symptomatic PAH classified as WHO functional class II or III and be able to walk between ≥ 150 m and ≤ 500 m in the 6MWT. In addition, the patients had to have a pulmonary vascular resistance of ≥ 5 WU and a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure of ≤ 15 mmHg. To be included in the study, patients had to be on stable doses of background PAH therapy for ≥ 90 days prior to screening and maintain these doses throughout the study.

The study included a total of 323 patients who were randomly allocated in a 1:1 ratio to sotatercept (N = 163) or placebo (N = 160). Randomization was stratified by WHO functional class (II versus III) and type of background therapy (mono/double versus triple therapy).

Treatment in the STELLAR study was divided into a primary treatment phase (double-blind placebo-controlled) and a long-term treatment phase (long-term double-blind) (see Figure 1). The duration of the primary treatment phase was 24 weeks. After completion of the primary treatment phase, patients continued their treatment according to randomization for up to 72 weeks, with blinding being maintained. After the last included patient had completed the primary treatment phase, the study was unblinded. Subsequently, all patients could receive sotatercept in the SOTERIA extension study [8]. In addition, early transition into the extension study was possible under the following conditions:

- after completion of the primary 24-week treatment phase, if clinical worsening had previously occurred without initiation of rescue therapy with an approved PAH therapy and without increasing the dose of infusion prostacyclin by ≥ 10%
- during the long-term treatment phase after discontinuation of therapy due to any clinical deterioration

The company did not provide any information on how many patients transitioned to the SOTERIA study and at what point in time.



During the LTDB treatment period, select study visits may be performed as home health care (HHC) visits.
LTDB treatment period will last until the last participant randomized completes the DBPC treatment period, at which point the study will be unblinded and participants may rollover to the LTFU study
LTDB treatment period duration is estimated based on projected enrollment duration and time required for the last participant to complete the DBPC treatment period.
Background PAH therapy refers to approved PAH-specific medications and may consist of monotherapy or combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase imulators, and/or prostacyclin analogues or receptor agonists.
Sotatercept at a starting dose of 0.3 mg/kg SC with a target dose of 0.7 mg/kg SC
Primary endpoint analysis will be completed after the last participant randomized completes the DBPC treatment period.

6MWD = 6-minute walk distance; EOS = end of study; EOT = end of treatment; PAH = pulmonary arterial hypertension.

Figure 1: Design of the STELLAR study [4]

Treatment with sotatercept was largely in compliance with the SPC [9]. For ≥ 90 days prior to screening, patients enrolled in the study had to be on stable doses of background PAH therapy, consisting of monotherapy or combination therapy with endothelin receptor antagonists, PDE5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues and/or selective prostacyclin receptor agonists. The patient-specific dose goal for each PAH therapy had to be already achieved at study entry. Background therapy had to remain stable throughout the study. If the patients experienced a clinical deterioration during the course of the study that required the initiation of rescue therapy with an approved PAH therapy or an increase in the dose of infusion prostacyclin by ≥ 10%, this led to discontinuation of the study medication. The addition of a diuretic or switching of an oral diuretic to parenteral administration was also not allowed throughout the study; however, dose adjustments in oral diuretics were allowed throughout the study.

The primary outcome of the STELLAR study was the change in 6MWT walking distance at Week 24 from baseline. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Data cut-offs

For the STELLAR study, 2 data cut-offs are available:

- 26 August 2022 (prespecified primary analysis after all patients had completed the first 24 weeks of study treatment)
- 6 December 2022 (prespecified final analysis at the end of the study)

For the benefit assessment, the company used analyses on the final data cut-off of 6 December 2022 for all outcomes.

I 3.2 Assessment of the evidence presented by the company

The analyses presented by the company are unsuitable for drawing conclusions on the added benefit of sotatercept in comparison with the ACT. This is further explained below.

Appropriate comparator therapy not implemented in the STELLAR study

For the present therapeutic indication, the G-BA defined individualized therapy with a choice of the several drugs as ACT (see also Table 4). The G-BA further specified the implementation of individualized therapy in its additional notes. According to these notes, it is assumed, among other things, that the continuous, subcutaneous, or intravenous use of prostacyclin analogues usually applies to advanced disease only, so that the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally, are not considered an ACT. Around 40% of patients in both study arms of the STELLAR study received treatment with

parenteral prostacyclin analogues, however. The ACT defined by the G-BA was therefore not implemented for a relevant proportion of patients.

Furthermore, irrespective of therapy with parenteral prostacyclin analogues, there are uncertainties as to whether the individualized therapy was adequately implemented in the STELLAR study. In its notes, the G-BA stated that continuation of an inadequate therapy does not constitute an implementation of the ACT. In the STELLAR study, sotatercept was compared with placebo, with patients in both study arms receiving background PAH therapy. Background therapy had to be stable for ≥ 90 days prior to screening and had to remain stable throughout the study. Hence, there was no treatment optimization at any time during the study.

According to the ESC/ERS guideline, the overarching treatment goal for patients with PAH is to achieve and maintain low-risk status [3]. At the start of the study, around 17% of patients in the comparator arm had a low-risk status according to the French Risk Score (WHO functional class I or II and 6MWT > 440 m, and N-terminal pro-brain natriuretic peptide (NT-proBNP) level < 300 ng/L). These patients would also be classified as low risk according to the 4-strata model of the current ESC/ERS guideline. A large proportion of the patients included in the comparator arm of the STELLAR study can therefore be assigned to an intermediate-low or intermediate-high mortality risk based on the risk stratification according to the 4-strata model of the ESC/ERS guideline. For patients with an intermediate-low or intermediate-high mortality risk, it can be assumed that there is a need for further optimization of PAH therapy [3].

In the comparator arm of the STELLAR study, 2.5% of patients received monotherapy, 34.4% of patients received combination therapy with 2 drugs, and 63.1% of patients received combination therapy with 3 drugs. For patients with dual therapy in particular, it is unclear whether therapy optimization was indicated at the start of the study or during the course of the study. For example, in the comparator arm of the STELLAR study, 38 patients (23.8%) received a combination therapy of one endothelin receptor antagonist and one PDE-5 inhibitor. The ESC/ERS guideline recommends further optimization of therapy by adding the selective prostacyclin receptor agonist selexipag or by switching from a PDE-5 inhibitor to the soluble guanylate cyclase stimulator riociguat in patients who have an intermediate-low risk despite initial dual therapy with one endothelin receptor antagonist and one PDE-5 inhibitor [3]. Due to a lack of information on the risk status of these patients, it cannot be assessed whether such a treatment optimization would also have been indicated in the patients who received a combination of one endothelin receptor antagonist and one PDE-5 inhibitor in the STELLAR study. On the basis of the available data, it is also not possible to assess whether it would have been meaningful to adjust the therapy for those patients who received a different combination of 2 drugs. It is also unclear whether other optimization options, such as switching from a PDE-5 inhibitor to riociguat, were available for patients on triple therapy. In

order to assess for how many patients in the comparator arm of the STELLAR study treatment optimization would have been meaningful and still possible, detailed information on the background PAH therapy based on the risk stratification would be necessary.

Furthermore, no information is available on the respective dosage of the drugs used in background therapy. The patient-specific dose goal for each PAH therapy had to be already achieved at study entry, but it is not possible to check the approval-compliant dosage of the drugs on the basis of the information available. It should also be noted that patient-specific concomitant medication with diuretics was only possible to a limited extent in the STELLAR study. Whereas the dose of oral diuretics could be adjusted during the course of the study, the addition of a diuretic or switching of an oral diuretic to parenteral administration was not allowed throughout the study.

As part of a patient-specific therapy, physiotherapeutic measures, if indicated, should also be made available to patients in both arms of the study in addition to drug therapy. It is questionable whether the patients in the STELLAR study had sufficient access to non-drug physiotherapeutic measures. In the STELLAR study, initiation of an exercise programme for cardiopulmonary rehabilitation was not allowed within 90 days prior to the screening visit or during the study. Only the continuation of an ongoing exercise programme as concomitant therapy during the study was permitted. During the study, 17 patients in the sotatercept arm (10%) and 22 patients in the comparator arm (14%) underwent an exercise programme for cardiopulmonary rehabilitation. For a further 43 patients in the sotatercept arm (26%) and 51 patients in the comparator arm (32%), it can be assumed that such an exercise programme would have been recommended but was not carried out because it was not reimbursable or not locally available. Based on the available data, it is also unclear to what extent other physiotherapeutic measures (e.g. physiotherapy, exercise treatment, respiratory therapy) were available to the patients in the study.

In summary, the analyses presented by the company on the total population of the STELLAR study are not suitable for the benefit assessment due to the lack of implementation of the ACT. It is unclear whether the study population of the STELLAR study includes a relevant subpopulation for which the ACT defined by the G-BA was adequately implemented.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of sotatercept in combination with other PAH therapies in adult patients with PAH with WHO functional class II to III, in comparison with the ACT. 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 summarized in Table 7.

Table 7: Sotatercept – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Treatment of PAH in adult patients with WHO functional class II to III, to improve exercise capacity[b, c]	Individualized therapy[d, e, f] taking into account prior therapies and health status, with a choice of the following therapies: ▪ endothelin receptor antagonists (ambrisentan, bosentan, macitentan) ▪ phosphodiesterase type 5 inhibitors (sildenafil, tadalafil) ▪ prostacyclin analogues (iloprost)[g] ▪ selective prostacyclin receptor agonists (selexipag) ▪ soluble guanylate cyclase stimulator (riociguat)	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients included in the study are not eligible for a lung transplant or a heart-lung transplant.
c. According to the G-BA, it can be inferred from the guideline recommendations that treatment with calcium antagonists alone is indicated if the patients have a positive vasoreactivity test. However, targeted PAH therapy (e.g. with endothelin receptor antagonists, phosphodiesterase type 5 inhibitors) is recommended for patients with a negative vasoreactivity test and for vasoreactive patients who no longer respond to treatment with calcium antagonists alone. Therefore, it is assumed that the patients included in the study are not eligible for treatment with calcium channel blockers alone.
d. For the implementation of individualized therapy in a study of direct comparison, the investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). Usually, combination therapies are used in the present therapeutic indication. If monotherapy is indicated in the comparator arm, this must be justified in the dossier. Continuation of an inadequate therapy does not constitute an implementation of the ACT. The sole dose optimization of a monotherapy or a change of drugs within a monotherapy does not correspond to the ACT.
e. According to the G-BA, there are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic measures can be indicated in the sense of both the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) and a targeted training therapy to improve performance (e.g. after a surgical treatment). Only patients without notable limitations of resilience are eligible for the specific training therapy to increase performance, while physiotherapeutic measures in the sense of the Remedies Directive (physical therapy such as physiotherapy, exercise treatment, and respiratory therapy) may be suitable for all patients. Physiotherapeutic measures, if indicated, should be made available to patients in both arms of the study in addition to drug therapy.
f. It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
g. Although the prostacyclin analogues treprostinil and epoprostenol, which are administered parenterally only, are approved for WHO/NYHA class III, it is assumed in accordance with the G-BA that the continuous, subcutaneous, or intravenous use of prostacyclin analogues usually applies to advanced disease only, so that this option is not considered an ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; WHO: World Health Organization

The assessment described above deviates from that of the company, which derived an indication of major added benefit on the basis of the data provided by the company.

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.

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