Sotatercept
(pulmonary arterial hypertension)

Addendum to Project A24-96
(dossier assessment)[1]

ADDENDUM

Project: A25-14 Version: 1.0 Status: 14 Feb 2025 DOI: 10.60584/A25-14_en

[1] Translation of the addendum *Sotatercept (pulmonale arterielle Hypertonie) – Addendum zum Projekt A24-96 (Dossierbewertung)*. 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) – Addendum to Project A24-96

Commissioning agency

Federal Joint Committee

Commission awarded on

28 January 2025

Internal Project No.

A25-14

https://doi.org/10.60584/A25-14_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
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Sotatercept (pulmonary arterial hypertension); Addendum to Project A24-96 (dossier assessment) [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-14_en.

Keywords

Sotatercept, Pulmonary Arterial Hypertension, Benefit Assessment, NCT04576988

IQWiG employees involved in the addendum

- Christian Siebel
- Moritz Felsch
- Prateek Mishra
- Daniela Preukschat
- Claudia Selbach

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
6MWT	6-minute walking test
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PAH	pulmonary arterial hypertension
PAH-SYMPACT	Pulmonary Arterial Hypertension – Symptoms and Impact
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale
WHO	World Health Organization

1 Background

On 28 January 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-96 (Sotatercept – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the STELLAR study, taking into account the data presented in the dossier [2] and by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [3,4].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The research question of benefit assessment A24-96 [1] was 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).

In its dossier, the company presented results on the total population of the randomized controlled trial (RCT) STELLAR [2]. Around 40% of patients in both study arms of the STELLAR study received treatment with the parenteral prostacyclin analogues treprostinil and epoprostenol. The parenteral prostacyclin analogues treprostinil and epoprostenol were not part of the ACT specified by the G-BA, however. Thus, the ACT specified by the G-BA was not implemented for a relevant proportion of patients in the STELLAR study. Furthermore, irrespective of therapy with parenteral prostacyclin analogues, there were uncertainties as to whether individualized therapy was adequately implemented in the STELLAR study. In addition, no information was available on the respective dosage of the drugs used as part of the background therapy, so that it was not possible to check whether the drug dosing in the study was in compliance with the approval.

Since the ACT was not implemented for a relevant proportion of the patients included, the STELLAR study was unsuitable for the benefit assessment. In compliance with the commission, the total population of the STELLAR study is assessed below.

2.1 Assessment of the STELLAR study

2.1.1 Study characteristics

The characteristics of the STELLAR study and of the study population can be found in dossier assessment A24-96 [1].

Treatment optimization in the comparator arm

Within the commenting procedure and following the oral hearing, the company subsequently submitted further data on individualized therapy in the STELLAR study [3,4]. In its comments, the company presented, among other things, information on background PAH therapy based on risk stratification, which showed that around a quarter of patients in the intervention versus comparator arm can be assigned to an intermediate-low to high risk and only received dual therapy despite not achieving the treatment goal (low-risk status). For these patients, it initially remained unclear whether it would have been possible to optimize treatment at the start of the study, e.g. by adding a third drug component (also apart from the parenteral prostacyclins). Following the oral hearing, the company submitted data showing that the addition of further drug therapy was either not recommended for a large proportion of patients who received mono- or dual therapy at the start of the study, or was not administered

due to safety/tolerability concerns (see Table 8 in Appendix A). In contrast, additional drug therapy was not reimbursable or not available for 8 patients in the intervention arm (4.9%) and 15 patients in the comparator arm (9.4%), which is why an uncertainty remains in the overall consideration, which is taken into account in the assessment of the certainty of conclusions (see below).

The company still did not provide any information on the dosage of the drugs used in the background therapy. However, it was emphasized in the commenting procedure that this was of secondary importance in the present therapeutic indication because the dosage of the used endothelin receptor antagonists and phosphodiesterase type 5 inhibitors was standardized [5,6]. Prostacyclin analogues, selective prostacyclin receptor agonists, and riociguat, on the other hand, are dosed individually [7-10]. There are no data to suggest that the dosage was not in compliance with the Summaries of Product Characteristics (SPCs). On the contrary, the subsequently submitted data on 19 patients who required therapy escalation with an approved background PAH therapy or an increase in the prostacyclin dose by at least 10% suggest that the drugs were largely dosed in compliance with the SPCs.

The remaining uncertainties regarding the implementation of individualized therapy are taken into account in the assessment of the certainty of conclusions (see Section 2.1.2.2).

Analysis periods

In the study, the primary analysis of the efficacy and side effects outcomes was planned at the time when all patients had completed the 24-week primary treatment phase. The data cut-off for this primary analysis was on 26 August 2022. The final data cut-off was at the end of the study on 6 December 2022 (date of the last visit of the last patient). Both data cut-offs were prespecified. After completion of the primary 24-week treatment phase, treatment of the patients in the respective study arms of the STELLAR study was continued for up to 72 weeks, and follow-up observation for up to 80 weeks, until the last patient included had completed the primary treatment phase (end of study). Due to the study design, the duration of treatment and observation in the STELLAR study varied from patient to patient. With the exception of the patient-reported outcomes on symptoms, health status and health-related quality of life, the outcomes in the study continued to be recorded after Week 24.

In Module 4 A and with the subsequently submitted data, the company presented analyses of the final data cut-off dated 6 December 2022, which refer to 2 different time periods depending on the outcome:

- Analysis period: at Week 24
- Analysis period: entire observation period until the end of the study

For this addendum, the entire observation period is considered based on the final data cut-off of the study. For the outcomes of walking ability and dyspnoea, as well as the patient-reported outcomes on symptoms, health status, and health-related quality of life, the company presented analyses for the analysis period at Week 24. The patient-reported outcomes on symptoms, health status and health-related quality of life were recorded at the start of treatment and at Week 24, so that the longest available observation period is available here. At Week 24, the outcomes of walking ability and dyspnoea were recorded in 97% of patients in the intervention arm and in 92% in the comparator arm, at Week 36 in 90% and 76%, and at Week 48 in only 51% and 33% of patients. Regardless of the markedly lower response rates, the descriptive analyses presented by the company in Appendix 4 G suggest that the results did not change notably after Week 24. Therefore, the analyses at Week 24 are considered for the outcomes of walking ability and dyspnoea as well as for the patient-reported outcomes on symptoms, health status and health-related quality of life.

Risk of bias across outcomes (study level)

Table 1 shows the risk of bias across outcomes (risk of bias at study level).

Table 1: Risk of bias across outcomes (study level) – RCT, direct comparison: sotatercept vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
STELLAR	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the STELLAR study is rated as low.

Transferability of the study results to the German health care context

The company described the STELLAR study with 91 study centres in 21 countries as an international and multicentre study. In Europe, patients were enrolled in 40 centres. According to the company, 9 centres in Germany enrolled 71 patients, corresponding to 22% of the patients in the STELLAR study.

The company also stated that the clear majority of patients were white (90.2% in the sotatercept arm and 88.1% in the placebo arm). According to the company, PAH is far more common in women, which is why the study included a majority of women. The patients had

had PAH for up to 40 years and the median duration of the disease was 7.26 years, which, according to the company, corresponds to the wide range also shown in German PAH patients who are eligible for treatment with sotatercept in compliance with the approval. Overall, the company considered the disease-specific characteristics of the study population to correspond to the German target population.

In the company's assessment, the recording of outcomes was standardized and had a low risk of bias, and it can therefore be assumed that the treatment effects observed in the STELLAR study are transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.1.2 Results

2.1.2.1 Presented outcomes

The following patient-relevant outcomes are presented in this addendum:

- Mortality
  - all-cause mortality
- Morbidity
  - walking ability, recorded with the 6-minute walking test (6MWT)
  - symptoms, recorded with the Pulmonary Arterial Hypertension – Symptoms and Impact (PAH-SYMPACT)
  - dyspnoea, recorded with the Borg CR10 scale
  - health status, recorded with the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded with the PAH-SYMPACT
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 2 shows the outcomes for which data were available from the study.

Table 2: Matrix of outcomes – RCT, direct comparison: sotatercept vs. placebo

Study	Outcomes									
	All-cause mortality[a]	Walking ability (6MWT)	Symptoms (PAH-SYMPACT)	Dyspnoea (Borg CR10 scale)	Health status (EQ-5D VAS)	Health-related quality of life (PAH-SYMPACT)	SAEs	Discontinuation due to AEs	Eye disorders (SOC, AEs)	Nose bleed (PT, AEs)
STELLAR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The results on all-cause mortality are based on the information on fatal AEs.

6MWT: 6-minute walking test; AE: adverse event; CR10: 10-point category ratio scale; PAH: pulmonary arterial hypertension; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

All-cause mortality

In Module 4 A of the dossier, the company presented analyses on all-cause mortality at Week 24. In the STELLAR study, however, the survival status was also recorded beyond Week 24, until the end of the study. Following the oral hearing, the company subsequently submitted analyses covering the entire study period. This addendum presents the data on deaths over the entire duration of the study. The difference between the observation periods in the 2 treatment arms (45.3 weeks versus 39.0 weeks) allows the consideration of the relative risk. The uncertainty resulting from the different observation periods, in particular due to the premature transition of patients from the STELLAR study to the SOTERIA extension study, is taken into account in the assessment of the risk of bias (see Section 2.1.2.2). The time-to-event analyses of overall survival in the STELLAR study presented by the company following the hearing also show no statistically significant differences between the treatment groups.

In addition to the analysis until Week 24, the company presented supplementary time-to-event analyses on overall survival in Module 4 A of the dossier, which, in addition to the observations over the entire course of the STELLAR study, also included the recordings of survival status in the single-arm extension study SOTERIA until the data cut-off on 8 November 2023. The company presented both an analysis adjusting for the treatment switch of patients from the placebo arm of the STELLAR study to treatment with sotatercept in the SOTERIA extension study (rank preserving structural failure time model), and an analysis without adjustment. However, the company did not present sufficient information on the 2 analyses for the assessment. It remains unclear how many patients from both treatment arms

transitioned into the SOTERIA extension study and how long the patients were observed in the extension study. It should also be noted that the data cut-off dated 8 November 2023 presented by the company is not a prespecified data cut-off. The supplementary analyses are therefore not presented.

Walking ability (6MWT)

For the dossier, the company conducted responder analyses of the improvement at Week 24 compared with baseline for the outcome of walking ability recorded using the 6MWT, using the post hoc defined response criterion of ≥ 40 m. No response threshold has been established for the 6MWT in the present therapeutic indication of PAH [11-14]. In addition, the response criterion of ≥ 40 m was not predefined. Furthermore, the company presented an analysis of the median difference between the treatment arms at Week 24 compared with baseline (Hodges-Lehman Location Shift) for the outcome of walking ability recorded with the 6MWT. The recording time points between baseline and Week 24 (Weeks 3 and 12) were not included in this analysis. This was the primarily planned analysis of the primary outcome in the STELLAR study. This addendum presents the prespecified analysis of the median difference between the treatment arms at Week 24.

Composite outcome of time to clinical worsening or death

The composite outcome of time to clinical worsening or death presented by the company comprises the following components:

- death
- listing for lung and/or heart transplant due to disease progression
- need to escalate therapy with an approved background PAH therapy or to increase the dose of infusion prostacyclin by ≥ 10%
- need for atrial septostomy
- hospitalization for disease progression (≥ 24 hours)
- deterioration of PAH defined by worsened WHO functional class and deterioration in 6MWT by ≥ 15% compared with baseline

For a composite outcome to be considered, the individual components of the outcome must be patient relevant. Simply adjusting the therapy for PAH is not patient relevant per se. Symptoms that require therapy adjustment and possible disadvantages of therapy adjustment should be reflected in other patient-relevant outcomes, however. In addition, the subcomponent of need to escalate therapy has an important influence on the result of the composite outcome. The composite outcome is therefore not presented in this addendum.

In Module 4 A of the dossier, the company additionally presented a sensitivity analysis that includes the components of death, listing for lung and/or heart transplant due to disease progression, need for atrial septostomy, hospitalization for disease progression (≥ 24 hours), and deterioration of PAH defined by deterioration in 6MWT by ≥ 40 m. This is a post hoc operationalization of the composite outcome specified for the dossier. The result of the composite outcome in this operationalization is notably influenced by events in the subcomponent of deterioration in 6MWT by ≥ 40 m. A deterioration in the 6MWT is already reflected by the change in the outcome of walking ability. As previously described for the outcome of walking ability, it should be noted that the response criterion of ≥ 40 m does not represent an established response threshold in the therapeutic indication and was not prespecified. The individual components of listing for lung and/or heart transplant due to disease progression, need for atrial septostomy, and hospitalization for disease progression (≥ 24 hours) are considered patient relevant. For the individual components, the company only presented results on the qualifying events, but not on all events that occurred in the individual components. Hence, no suitable data are available for the individual components.

Symptoms and health-related quality of life (PAH-SYMPACT)

The PAH-SYMPACT is a validated questionnaire for recording symptoms and health-related quality of life in patients with PAH [15,16]. The PAH-SYMPACT consists of 2 domains on symptoms (cardiopulmonary symptoms and cardiovascular symptoms) and 2 domains on the impacts of the disease (physical impacts and cognitive/emotional impacts). There is also one further question about oxygen use. Patients answered the questions on symptoms daily over a period of 7 days prior to the respective study visits. The questions on the impacts of the disease were answered on the last day of the 7-day period. The severity of the symptoms or the severity of the impacts of the disease were rated on a 5-point scale (0: none; 4: very severe). For the individual domains, the company presented responder analyses on improvement at Week 24 compared with baseline using the response criterion of 15% of the scale range. The patients included in the STELLAR study were symptomatic at baseline (WHO functional class II to III) and showed physical and cognitive/emotional impairments. Since additional treatment with sotatercept can therefore in principle improve symptoms and health-related quality of life, the analyses of the improvement at Week 24 are considered in each case.

Dyspnoea (Borg CR10 scale)

In the STELLAR study, the patients' dyspnoea was recorded using a Borg CR10 scale. Patients were asked to indicate their perceived dyspnoea before and after the 6MWT on the Borg CR10 scale (0: "no dyspnoea at all", 10: "extreme dyspnoea"). In Module 4 A of the dossier, the company presented responder analyses on the improvement in dyspnoea at Week 24 compared with baseline using the response criterion of 15% of the scale range. The company only considered the recording of perceived dyspnoea before conducting the 6MWT. As

previously described, the patients included in the STELLAR study were symptomatic at baseline. For the Borg CR10 scale, the analysis of the improvement at Week 24 is therefore considered.

Side effects

The analyses of AEs include events that can be attributed to both side effects and symptoms or late complications of the underlying disease. However, since the overall rates of SAEs and discontinuations due to AEs include only a few events overall that can be clearly attributed to the underlying disease, this is of no consequence for the present addendum.

Severe AEs

In the STELLAR study, the severity of AEs was assessed based on categories defined by the company rather than an established classification. This is not an adequate operationalization of severity. For this reason, the outcome is not presented.

2.1.2.2 Risk of bias

Table 3 describes the risk of bias for the results of the relevant outcomes.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sotatercept vs. placebo

Study	Study level	Outcomes									
		All-cause mortality[a]	Walking ability (6MWT)	Symptoms (PAH-SYMPACT)	Dyspnoea (Borg CR10 scale)	Health status (EQ-5D VAS)	Health-related quality of life (PAH-SYMPACT)	SAEs	Discontinuation due to AEs	Eye disorders (SOC, AEs)	Nose bleed (PT, AEs)
STELLAR	L	H[b]	L	H[c]	L	H[c]	H[c]	H[b]	L[d]	H[b]	H[b]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Incomplete observations for potentially informative reasons.
c. Large proportion of patients (> 10%) not considered in the analysis.
d. Despite the low risk of bias, a limited certainty of results is presumed for the outcome of discontinuation due to AEs.

6MWT: 6-minute walking test; AE: adverse event; CR10: 10-point category ratio scale; H: high; L: low; PAH: pulmonary arterial hypertension; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Due to incomplete observations for potentially informative reasons, the outcome-specific risk of bias for the results on the outcomes of all-cause mortality, SAEs, eye disorders, and nose bleed is rated as high. For example, it is unclear how many patients switched prematurely

from the STELLAR study to the SOTERIA extension study due to clinical deterioration and at what time points this occurred. For the results of the patient-reported outcomes of symptoms, health status, and health-related quality of life, the high risk of bias results from the high proportion of patients excluded from the analysis.

The risk of bias of the results for the outcomes of walking ability and dyspnoea at Week 24 is rated as low.

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. Consequently, after treatment discontinuation for other reasons, AEs that would have led to discontinuation may have occurred, but the criterion of discontinuation can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

As already described in Section 2.1.1, there are still uncertainties regarding the optimal titration of background PAH therapy in the STELLAR study. The information provided by the company in the commenting procedure shows that additional drug therapy would have been an option for 8 patients in the intervention arm (4.9%) and 15 patients in the comparator arm (9.4%) who were receiving monotherapy or dual therapy at baseline. In addition, hardly any information is available on the dosage of the drugs used as part of the background therapy, so that it was only possible to check approximately and in a small sample whether the drugs in the study were dosed in compliance with the approval. Overall, this reduces the certainty of conclusions of the study results.

2.1.2.3 Results

Table 4 and Table 5 summarize the results of the comparison of sotatercept with placebo in patients with WHO functional class II to III PAH . Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

The results on common AEs, SAEs and discontinuations due to AEs are presented in Appendix B.

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sotatercept vs. placebo (multipage table)

Study Outcome category Outcome	Sotatercept N	Sotatercept Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Sotatercept vs. placebo RR [95% CI]; p-value[a]
STELLAR					
Mortality					
All-cause mortality[b]	163	2 (1.2)	160	7 (4.4)	0.28 [0.06; 1.33]; 0.097[c]
Morbidity					
Symptoms (PAH-SYMPACT – improvement at Week 24[d])					
Cardiopulmonary symptoms	115	47 (40.9)	117	35 (29.9)	1.35 [0.95; 1.93]; 0.095
Cardiovascular symptoms	115	49 (42.6)	117	34 (29.1)	1.48 [1.04; 2.11]; 0.030
Dyspnoea (Borg CR10 scale – improvement at Week 24[e])	160	38 (23.8)	159	37 (23.3)	1.02 [0.69; 1.51]; 0.918
Health status (EQ-5D VAS – improvement at Week 24[f])	124	29 (23.4)	126	20 (15.9)	1.49 [0.89; 2.49]; 0.131
Health-related quality of life					
PAH-SYMPACT – improvement at Week 24[d]					
Physical impacts	117	39 (33.3)	123	31 (25.2)	1.31 [0.87; 1.96]; 0.193
Cognitive/emotional impacts	117	30 (25.6)	123	30 (24.4)	1.04 [0.67; 1.60]; 0.866
Side effects					
AEs (supplementary information)	163	151 (92.6)	160	149 (93.1)	–
SAEs	163	40 (24.5)	160	47 (29.4)	0.84 [0.58; 1.20]; 0.529[c]
Discontinuation due to AEs	163	6 (3.7)	160	11 (6.7)	0.54 [0.20; 1.41]; 0.246[c]
Eye disorders (SOC, AEs)[g]	163	21 (12.9)	160	7 (4.4)	2.94 [1.29; 6.73]; 0.007[c]
Nose bleed (PT, AEs)	163	36 (22.1)	160	3 (1.9)	11.78 [3.70; 37.48]; < 0.001[c]

Table 4: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sotatercept vs. placebo (multipage table)

Study Outcome category Outcome	Sotatercept N	Sotatercept Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Sotatercept vs. placebo RR [95% CI]; p-value[a]
a. Unless otherwise stated: Mantel-Haenszel estimate, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy); p-value of Wald test. b. The results on all-cause mortality are based on the data on fatal AEs over the entire course of the study. c. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [17]). d. A decrease by ≥ 0.6 points from baseline is considered a clinically relevant improvement (scale range: 0 to 4). e. A decrease by ≥ 1.5 points from baseline is considered a clinically relevant improvement (scale range: 0 to 10). f. An increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100). g. Common events in the intervention vs. control arm were blurred vision (4 vs. 0) and cataract (4 vs. 0). 6MWT: 6-minute walking test; AE: adverse event; CI: confidence interval; CR10: 10-point category ratio scale; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; PAH: pulmonary arterial hypertension; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; WHO: World Health Organization					

Table 5: Results (morbidity, continuous) – RCT, direct comparison: sotatercept vs. placebo

Study Outcome category Outcome	Sotatercept N[a]	Sotatercept Values at baseline [m] median [Q1; Q3]	Sotatercept Median change by Week 24 [m] mean (min; max)[b]	Placebo N[a]	Placebo Values at baseline [m] median [Q1; Q3]	Placebo Median change by Week 24 [m] mean (min; max)[b]	Sotatercept vs. placebo Hodges-Lehman Location Shift [95% CI]; p-value
STELLAR							
Morbidity							
Walking ability (6MWT) at Week 24	163	417.0 (348.0; 464.5)	34.3 (33.0; 35.5)	160	427.1 (365.0; 465.0)	1.0 (-1.0; 3.5)	40.40 [27.28; 53.53]; < 0.001
a. Number of patients taken into account in the effect estimation; baseline values (and values at Week 24) may rest on different patient numbers. b. Mean, minimum and maximum of the median changes at Week 24 resulting from the imputation data sets generated by multiple imputation. 6MWT: 6-minute walking test; CI: confidence interval; m: metre; max: maximum; min: minimum; N: number of analysed patients; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial							

As described in Section 2.1.2.2, the certainty of conclusions on all outcomes is limited.

Mortality

All-cause mortality

No statistically significant difference between treatment groups was found for the outcome of all-cause mortality.

Morbidity

Walking ability (6MWT)

For the outcome of walking ability, recorded with the 6MWT, a statistically significant difference between treatment groups was found at Week 24 in favour of sotatercept. However, there is an effect modification by the characteristic of WHO functional class. For patients with WHO functional class II PAH, a statistically significant difference was found in favour of sotatercept compared with placebo, but this is not rated as clinically relevant. For patients with WHO functional class III PAH, however, a statistically significant and clinically relevant difference between treatment groups was found in favour of sotatercept (see Section 2.1.2.4).

Symptoms (PAH-SYMPACT)

Cardiopulmonary symptoms

No statistically significant difference between treatment groups was found at Week 24 for the outcome of cardiopulmonary symptoms.

Cardiovascular symptoms

For the outcome of cardiovascular symptoms, a statistically significant difference between treatment groups was found at Week 24 in favour of sotatercept.

Dyspnoea (Borg CR10 scale)

No statistically significant difference between treatment groups was found at Week 24 for the outcome of dyspnoea, measured with the Borg CR10 scale.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status, recorded with the EQ-5D VAS, at Week 24. However, there is an effect modification by the characteristic of WHO functional class. For patients with WHO functional class II PAH, there is a statistically significant difference in favour of sotatercept compared with placebo. For patients with WHO functional class III PAH, however, there is no statistically significant difference between the treatment groups (see Section 2.1.2.4).

Health-related quality of life (PAH-SYMPACT)

Health-related quality of life was recorded using the PAH-SYMPACT domains of physical impacts and cognitive/emotional impacts.

No statistically significant difference between treatment groups was shown at Week 24 for the outcomes of physical impacts or cognitive/emotional impacts.

Side effects

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs.

Eye disorders (AEs)

A statistically significant difference between treatment groups to the disadvantage of sotatercept was found for the outcome of eye disorders (AEs).

Nose bleed (AEs)

A statistically significant difference between treatment groups to the disadvantage of sotatercept was found for the outcome of nose bleed (AEs).

2.1.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the present addendum:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- WHO functional class II versus III

The company submitted subgroup analyses by age, sex and WHO functional class for all outcomes listed in the dossier, with the exception of the outcome of all-cause mortality. The company justified this with the fact that the number of events for the outcome of all-cause mortality is below the threshold of 10 events. The company's approach is appropriate.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 6 and Table 7 summarize the subgroup results of the comparison of sotatercept with placebo in patients with WHO functional class II to III PAH.

Table 6: Subgroups (morbidity, continuous) – RCT, direct comparison: sotatercept vs. placebo

Study **Outcome**	**Sotatercept**			**Placebo**			**Sotatercept vs. placebo**
Characteristic **Subgroup**	**N[a]**	**Values at baseline [m] median [Q1; Q3]**	**Median change by Week 24 [m] mean (min; max)[b]**	**N[a]**	**Values at baseline [m] median [Q1; Q3]**	**Median change by Week 24 [m] mean (min; max)[b]**	**Hodges-Lehman Location Shift [95% CI]; p-value**
STELLAR							
Walking ability (6MWT) at Week 24							
Disease severity							
WHO FC II	79	ND	ND	78	ND	ND	21.6 [6.67; 36.60]; ND
WHO FC III	84	ND	ND	82	ND	ND	60.9 [40.46; 81.35]; ND
Total						Interaction:	0.002[c]

a. Number of patients taken into account in the effect estimation; baseline values (and values at Week 24) may rest on different patient numbers.
b. Mean, minimum and maximum of the median changes at Week 24 resulting from the imputation data sets generated by multiple imputation.
c. p-value of Cochran's Q test.

6MWT: 6-minute walking test; CI: confidence interval; m: metre; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; WHO: World Health Organization; WHO FC: WHO functional class

Table 7: Subgroups (morbidity, dichotomous) – RCT, direct comparison: sotatercept vs. placebo

Study Outcome Characteristic Subgroup	Sotatercept N	Sotatercept Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Sotatercept vs. placebo RR [95% CI]	Sotatercept vs. placebo p-value
STELLAR						
Morbidity						
Health status (EQ-5D VAS[a]; improvement at Week 24)						
Disease severity						
WHO FC II	65	16 (24.6)	65	5 (7.7)	3.20 [1.24; 8.26][b]	0.016
WHO FC III	59	13 (22.0)	61	15 (24.6)	0.91 [0.48; 1.73][b]	0.764
Total					Interaction: 0.026[c]	

a. An increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100).
b. RR: Mantel-Haenszel estimate, stratified by WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy); p-value: Wald test.
c. p-value of the likelihood ratio test, based on a linear model (according to the company) with the covariates treatment and subgroup as well as the interaction between treatment and subgroup, which is stratified according to WHO functional class (class II vs. III) and background PAH therapy (mono/double vs. triple therapy).

AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class; WHO: World Health Organization; WHO FC: WHO functional class

Morbidity

Walking ability (6MWT)

There is an effect modification by the characteristic of WHO functional class for the outcome of walking ability (6MWT).

For patients with WHO functional class II PAH a statistically significant difference was found between treatment groups in favour of sotatercept. However, the lower limit of the 95% confidence interval is only 6.7 m, which is not classified as clinically relevant.

For patients with WHO functional class III PAH, there is also a statistically significant difference between the treatment groups. The lower limit of the 95% confidence interval is 40.5 m, which is interpreted as a relevant effect. There is an advantage of sotatercept over placebo.

Health status (EQ-5D VAS)

There is an effect modification by the characteristic of WHO functional class for the outcome of health status (EQ-5D VAS). For patients with WHO functional class II PAH a statistically significant difference was found between treatment groups in favour of sotatercept.

For patients with WHO functional class III PAH, no statistically significant difference was found between treatment groups, however.

2.1.3 Summary of the results

Based on the STELLAR study, there are the following advantages and disadvantages at outcome level for adult patients with WHO functional class II to III PAH:

- advantage of sotatercept versus placebo for the outcome of walking ability (6MWT) at Week 24 in the subgroup of patients with WHO functional class III PAH
- advantage of sotatercept versus placebo for the outcome of health status (EQ-5D VAS) at Week 24 in the subgroup of patients with WHO functional class II PAH
- advantage of sotatercept versus placebo for the outcome of cardiovascular symptoms (PAH-SYMPACT) at Week 24
- disadvantages of sotatercept versus placebo for the outcomes of eye disorders (AEs) and nose bleed (AEs)

The G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Sotatercept (pulmonale arterielle Hypertonie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2024 [Accessed: 16.12.2024]. URL: https://doi.org/10.60584/A24-96.

2. MSD Sharp & Dohme. Sotatercept (WINREVAIR); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2024 [Accessed: 20.01.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1125/#dossier.

3. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr. 1898: Sotatercept (pulmonale arterielle Hypertonie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1125/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr. 1898: Sotatercept (pulmonale arterielle Hypertonie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Zusatzanalyse im Nachgang zur mündlichen Anhörung [unpublished]. 2025.

5. Deutsche Gesellschaft für Kardiologie, Deutschen Gesellschaft für Pneumologie. Stellungnahme zum IQWiG-Bericht Nr. 1898: Sotatercept (pulmonale arterielle Hypertonie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1125/#beschluesse in the document "Zusammenfassende Dokumentation"].

6. Gemeinsamer Bundesausschuss. Sotatercept (D-1104); mündliche Anhörung gemäß 5. Kapitel § 19 Abs. 2 Verfahrensordnung

des Gemeinsamen Bundesausschusses - stenografisches Wortprotokoll [online]. 2025 [Accessed: 07.02.2025]. URL: https://www.g-ba.de/downloads/91-1031-1125/2025-01-27_Wortprotokoll_Sotatercept_D-1104.pdf.

7. Johnson&Johnson. Uptravi Filmtabletten [online]. 12.2024 [Accessed: 10.02.2025]. URL: https://www.fachinfo.de.

8. Janssen-Cilag. VELETRI 0,5 mg/-1,5mg Pulver zur Herstellung einer Infusionslösung [online]. 11.2022 [Accessed: 07.02.2025]. URL: https://www.fachinfo.de.

9. OMT. REMODULIN 5 mg/ml Infusionslösung [online]. 07.2021 [Accessed: 07.02.2025]. URL: https://www.fachinfo.de.

10. MSD. Adempas 0,5 mg/–1 mg/–1,5 mg/–2 mg/–2,5 mg Filmtabletten [online]. 05.2023 [Accessed: 07.02.2025]. URL: https://www.fachinfo.de.

11. Moutchia J, McClelland RL, Al-Naamani N et al. Minimal Clinically Important Difference in the 6-minute-walk Distance for Patients with Pulmonary Arterial Hypertension. Am J Respir Crit Care Med 2023; 207(8): 1070-1079. https://doi.org/10.1164/rccm.202208-1547OC.

12. Mathai SC, Puhan MA, Lam D et al. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2012; 186(5): 428-433. https://doi.org/10.1164/rccm.201203-0480OC.

13. Gabler NB, French B, Strom BL et al. Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. Circulation 2012; 126(3): 349-356. https://doi.org/10.1161/CIRCULATIONAHA.112.105890.

14. Gilbert C, Brown MCJ, Cappelleri JC et al. Estimating a minimally important difference in pulmonary arterial hypertension following treatment with sildenafil. Chest 2009; 135(1): 137-142. https://doi.org/10.1378/chest.07-0275.

15. McCollister D, Shaffer S, Badesch DB et al. Development of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT(R)) questionnaire: a new patient-reported outcome instrument for PAH. Respir Res 2016; 17(1): 72. https://doi.org/10.1186/s12931-016-0388-6.

16. Chin KM, Gomberg-Maitland M, Channick RN et al. Psychometric Validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Questionnaire: Results of the SYMPHONY Trial. Chest 2018; 154(4): 848-861. https://doi.org/10.1016/j.chest.2018.04.027.

17. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

Appendix A Reasons why no additional drug therapy was used at the start of the study for study participants with monotherapy or dual therapy

Table 8: Reasons why no additional drug therapy was used in study participants with monotherapy or dual therapy – RCT, direct comparison: sotatercept vs. placebo

Study	**n (%)**	
Type of background therapy **Reasons**	**Sotatercept** **N = 163**	**Placebo** **N = 160**
STELLAR		
Monotherapy	9 (5.5)	4 (2.5)
Additional drug therapy not recommended	2 (1.2)	2 (1.3)
Additional drug therapy not reimbursable/not available	3 (1.8)	1 (0.6)
Safety/tolerability concerns	4 (2.5)	1 (0.6)
Dual therapy	56 (34.4)	56 (35.0)
Additional drug therapy refused by the patient	4 (2.5)	6 (3.8)
Additional drug therapy not recommended	31 (19.0)	16 (10.0)
Additional drug therapy not reimbursable/not available	5 (3.1)	14 (8.8)
Safety/tolerability concerns	16 (9.8)	20 (12.5)

n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial

Appendix B Results on side effects

For the overall rates of AEs and SAEs, the tables below present events for Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) and PTs, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rate of SAEs: events that occurred in at least 5% of the patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 9: Common AEs[a] – RCT, direct comparison: sotatercept vs. placebo (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Sotatercept** **N = 163**	**Placebo** **N = 160**
STELLAR		
Overall AE rate	151 (92.6)	149 (93.1)
Blood and lymphatic system disorders	29 (17.8)	25 (15.6)
Thrombocytopenia	16 (9.8)	3 (1.9)
Cardiac disorders	30 (18.4)	30 (18.8)
Ear and labyrinth disorders	13 (8.0)	14 (8.8)
Eye disorders	21 (12.9)	7 (4.4)
Gastrointestinal disorders	68 (41.7)	51 (31.9)
Diarrhoea	25 (15.3)	16 (10.0)
Nausea	23 (14.1)	19 (11.9)
General disorders and administration site conditions	61 (37.4)	50 (31.3)
Fatigue	23 (14.1)	16 (10.0)
Injection site pain	11 (6.8)	11 (6.9)
Peripheral oedema	14 (8.6)	12 (7.5)
Immune system disorders	11 (6.8)	7 (4.4)
Infections and infestations	105 (64.4)	89 (55.6)
COVID-19	48 (29.5)	42 (26.3)
Nasopharyngitis	11 (6.8)	13 (8.1)
Upper respiratory tract infection	9 (5.5)	11 (6.9)
Urinary tract infection	11 (6.8)	6 (3.8)
Injury, poisoning and procedural complications	27 (16.6)	19 (11.9)
Investigations	33 (20.3)	21 (13.1)
Haemoglobin increased	10 (6.1)	0 (0)
Metabolism and nutrition disorders	37 (22.7)	33 (20.6)
Hypokalaemia	14 (8.6)	6 (3.8)
Iron deficiency	11 (6.8)	9 (5.6)
Musculoskeletal and connective tissue disorders	50 (30.7)	30 (18.8)
Nervous system disorders	62 (38)	40 (25.0)
Dizziness	24 (14.7)	10 (6.3)
Headache	40 (24.5)	28 (17.5)
Psychiatric disorders	13 (8.0)	8 (5.0)
Renal and urinary disorders	7 (4.3)	12 (7.5)

Table 9: Common AEs[a] – RCT, direct comparison: sotatercept vs. placebo (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Sotatercept N = 163**	**Placebo N = 160**
Reproductive system and breast disorders	10 (6.1)	10 (6.3)
Respiratory, thoracic and mediastinal disorders	59 (36.2)	48 (30.0)
Dyspnoea	5 (3.1)	17 (10.6)
Nose bleed	36 (22.1)	3 (1.9)
Nasal congestion	10 (6.1)	0 (0)
Skin and subcutaneous tissue disorders	65 (39.9)	31 (19.4)
Rash	13 (8.0)	6 (3.8)
Telangiectasia	27 (16.6)	7 (4.4)
Vascular disorders	27 (16.6)	16 (10.0)
Irrigation	10 (6.1)	4 (2.5)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 10: Common SAEs[a] – RCT, direct comparison: sotatercept vs. placebo

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Sotatercept N = 163**	**Placebo N = 160**
STELLAR		
Overall SAE rate	40 (24.5)	47 (29.4)
Cardiac disorders	6 (3.7)	11 (6.9)
Infections and infestations	14 (8.6)	8 (5)
Respiratory, thoracic and mediastinal disorders	7 (4.3)	11 (6.9)

a. Events that occurred in at least one study arm in ≥ 5% of patients.
b. MedDRA version 25.0; SOC and PT notation taken from Module 4.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 11: Discontinuation due to AEs – RCT, direct comparison: sotatercept vs. placebo

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Sotatercept** **N = 163**	**Placebo** **N = 160**
STELLAR		
Overall rate of discontinuations due to AEs	6 (3.7)	11 (6.9)
Cardiac disorders	1 (0.6)	3 (1.9)
Cardiac arrest	0 (0)	2 (1.3)
Right ventricular failure	0 (0)	1 (0.6)
Acute myocardial infarction	1 (0.6)	0 (0)
Immune system disorders	1 (0.6)	0 (0)
Sarcoidosis	1 (0.6)	0 (0)
Infections and infestations	0 (0)	2 (1.3)
COVID-19 pneumonia	0 (0)	1 (0.6)
Sepsis	0 (0)	1 (0.6)
Metabolism and nutrition disorders	0 (0)	1 (0.6)
Malnutrition	0 (0)	1 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.6)	0 (0)
Arthralgia	1 (0.6)	0 (0)
Nervous system disorders	1 (0.6)	0 (0)
Haemorrhage intracranial	1 (0.6)	0 (0)
Pregnancy, puerperium and perinatal conditions	0 (0)	1 (0.6)
Pregnancy termination	0 (0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	2 (1.2)	4 (2.5)
Pulmonary arterial hypertension	0 (0)	2 (1.3)
Pulmonary hypertension	0 (0)	1 (0.6)
Respiratory failure	0 (0)	1 (0.6)
Nose bleed	1 (0.6)	0 (0)
Haemoptysis	1 (0.6)	0 (0)
Skin and subcutaneous tissue disorders	1 (0.6)	0 (0)
Telangiectasia	1 (0.6)	0 (0)

a. MedDRA version 25.0; SOC and PT notation taken from Module 4.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class