Sotatercept (pulmonary arterial hypertension, WHO functional class IV)

Addendum to Project A26-12 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

Project: A26-75 Version: 1.1 Status: 17 Jul 2026 DOI: 10.60584/A26-75_V1.1_en

[1] Translation of the addendum *Sotatercept (pulmonale arterielle Hypertonie, WHO-Funktionsklasse IV) – Addendum zum Projekt A26-12 (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, WHO functional class IV) – Addendum to Project A26-12

Commissioning agency

Federal Joint Committee

Commission awarded on

23 June 2026

Internal Project No.

A26-75

DOI-URL

https://doi.org/10.60584/A26-75_V1.1_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Sotatercept (pulmonary arterial hypertension, WHO functional class IV); Addendum to Project A26-12 (dossier assessment) [online]. 2026 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A26-75_V1.1_en.

Keywords

Sotatercept, Pulmonary Arterial Hypertension, Benefit Assessment, NCT04896008

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List of abbreviations

Abbreviation	Meaning
6MWT	6-minute walk test
ACT	appropriate comparator therapy
AE	adverse event
CR10	10-point category ratio scale
ERA	endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PAH	pulmonary arterial hypertension
PCA	prostacyclin analogue
PDE5I	Phosphodiesterase type 5 inhibitors
PRA	prostacyclin receptor agonist
RCT	randomized controlled trial
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
sGC	soluble guanylate cyclase
SmPC	summary of product characteristics
WHO	World Health Organization

1 Background

On 23 June 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A26-62 (Sotatercept – Benefit assessment according to §35a Social Code Book V) [1].

The commission assesses the suitability of the ZENITH study [2-7] for the research question of the benefit assessment, where appropriate, the analysis of the study, taking into account the documents subsequently submitted by the company as part of the commenting procedure. According to the G-BA, the following notes must be taken into account:

- Instead of parenteral epoprostenol, parenteral treprostinil may also be accepted as part of the triple therapy (prostacyclin analogue [PCA] + endothelin receptor antagonist [ERA] + phosphodiesterase type 5 inhibitor [PDE5I]).
- Where study participants receive combination therapy without parenteral PCA, the fact that these individuals are not suitable for treatment with parenteral PCA must be documented and discussed in the dossier of the benefit assessment.
- If, at the start of the study, further treatment escalation is not an option for patients, this must be documented and justified in the dossier.

The responsibility for this 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.

1.1 Changes in comparison with Version 1.0

The present Version 1.1 of 17 July 2026 replaces Version 1.0 of the addendum of 10 July 2026. The following change was made in Version 1.1 compared with Version 1.0:

- In Table 7 of Version 1.0 of the addendum, the number of analysed patients in the comparator arm for each of the three components of the outcome disease worsening is incorrectly stated as 20. This was corrected in Table 7 of this Version 1.1 of the addendum.

This change has no impact on the conclusion of the benefit assessment.

2 Assessment

The research question of dossier assessment A26-12 [1] was to assess the added benefit of sotatercept in combination with other pulmonary arterial hypertension (PAH) therapies compared with epoprostenol in combination with ERA (ambrisentan, bosentan, macitentan) and PDE5is (sildenafil, tadalafil) as appropriate comparator therapy (ACT) in adults with World Health Organization (WHO) functional class (FC) IV PAH.

In its dossier, the company presented results on the subpopulation with WHO-FC IV from the randomized controlled trial (RCT) ZENITH [8]. The ZENITH study is a completed, multicentre, double-blind RCT comparing sotatercept with placebo, each in addition to background PAH therapy, in adults with WHO FC III or IV PAH and at high risk of mortality. The available data showed that at least 45% of patients in the subpopulation with WHO FC IV in the ZENITH study did not receive epoprostenol. No reasons were given for this.

As part of the commenting procedure, the company provided, amongst other things, data of the drug combinations used, as well as the reasons for not using triple therapy [9]. In addition, the G-BA stipulated that parenteral treprostinil may also be accepted as an alternative to epoprostenol as part of the triple therapy (PCA + ERA + PDE5I).

This addendum examined the suitability of the ZENITH study for the research question of the benefit assessment and the analysis of the study, taking into account the documents subsequently submitted by the company within the framework of the commenting procedure, as well as further notes on the ACT.

2.1 Implementation of the ACT in the ZENITH study

On the basis of the information provided by the company in the commenting procedure, this addendum assesses the extent to which the ACT specified by the G-BA was implemented in the relevant subpopulation with WHO FC IV in the ZENITH study.

Table 1 shows the drug combinations used in the ZENITH study for background PAH therapy for PAH, as well as the reasons for not receiving triple therapy.

Table 1; Information on background PAH therapy at baseline (subpopulation with WHO FC IV) – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study **type of therapy** **drug combination** **drug**	**Patients with background PAH therapy at baseline, n (%)**	
	sotatercept + background therapy **N = 20**	**placebo + background therapy** **N = 24**
ZENITH		
Triple therapy	14 (70.0)	17 (70.8)
Parenteral PCA + ERA + PDE5I	7 (35.0)[a]	7 (29.2)[a]
Epoprostenol	3 (15.0)	1 (4.2)
Treprostinil	4 (20.0)[a]	6 (25.0)[a]
Parenteral PCA + ERA + sGC	3 (15.0)[a]	4 (16.7)[a]
Epoprostenol	0 (0)	0 (0)
Treprostinil	3 (15.0)[a]	4 (16.7)[a]
Inhaled / oral PCA[b] / PRA + ERA + PDE5I	3 (15.0)[a]	5 (20.8)[a]
Inhaled / oral PCA[b] / PRA + ERA + sGC	1 (5.0)[a]	1 (4.2)[a]
Dual therapy	6 (30.0)	7 (29.2)
With parenteral PCA	1 (5.0)[a]	2 (8.3)[a]
Epoprostenol	0 (0)	1 (4.2)
Treprostinil	1 (5.0)[a]	1 (4.2)[a]
With inhaled / oral PCA[b] / PRA	1 (5.0)[a]	2 (8.3)[a]
Without PCA / PRA	4 (20.0)[a]	3 (12.5)[a]
ERA + PDE5I	2 (10.0)	2 (8.3)
Reasons for not receiving triple therapy		
Concerns regarding tolerability	5 (25.0[a])	3 (12.5[a])
Lack of availability or reimbursement	1 (5.0[a])	3 (12.5[a])
Refusal by the patient	0 (0)	1 (4.2[a])

a. Institute's calculation.
b. Inhaled and oral treprostinil are not approved in Germany. In total, 0 versus 1 patient on triple therapy and 1 versus 1 patient on dual therapy received inhaled or oral treprostinil.

ERA: endothelin receptor antagonists; FC: functional class; n: number of patients with subsequent therapy; N: number of analysed patients; PCA: prostacyclin analogues; PDE5I: phosphodiesterase-5 inhibitors; PRA: prostacyclin receptor agonist; RCT: randomized controlled trial; sGC: soluble guanylate cyclase stimulator

According to the inclusion criteria of the ZENITH study, stable background therapy (dual or triple therapy) at the maximum tolerated dose, as assessed by the investigator, should be administered in both study arms at the start of the study. The background therapy was not part of the study medication. The information provided by the company as part of the commenting procedure shows that some patients had not received triple therapy, partly due

to a lack of availability or reimbursement. Treatment escalation would have been possible and medically indicated for these patients. Therefore, the inclusion criterion of a maximum tolerated background therapy alone did not directly mean that treatment escalation was generally no longer possible.

7 patients (approx. 29%) in the placebo arm received dual therapy. For three patients, concerns about tolerability were cited as the reason, and one patient had decided against triple therapy. For these four patients (approx. 17%), there is a valid reason why they did not receive the drug combination specified in the ACT. Three patients (approx. 13%) did not receive triple therapy due to a lack of availability or eligibility for reimbursement.

17 patients (approx. 71%) in the placebo arm received triple therapy with PCA. In 7 patients (approx. 29%), the drugs used (parenteral PCA + ERA + PDE5I) correspond to the drug combination specified by the G-BA. A further four patients (approx. 17%) received riociguat, a soluble guanylate cyclase (sGC) stimulator, instead of a PDE5 inhibitor. According to the ESC/ERS guideline [10], switching from PDE5Is to sGC constitutes a treatment escalation. Like treatment with ERA and PDE5I, treatment with sGC is approved for WHO FCs II and III, but is not explicitly approved for WHO FC IV. The G-BA's notes on the ACT state that continuation of treatment options approved for less severe WHO FCs should remain available. An implementation of the ACT does therefore not require a re-switch of these patients to PDE5Is. A further 6 patients (25%) in the placebo arm received triple therapy with inhaled or oral PCA or a PRA. It is unclear whether the reason these patients did not switch to a parenteral PCA was due to concerns about tolerability, patient request, or a lack of availability or eligibility for reimbursement. As the reasons for the use or non-use of certain drug classes in triple therapy were not documented in the ZENITH study, it is not clear from the available data whether it would still have been possible to escalate treatment for individual patients in triple therapy using parenteral PCA.

In its comments, the company provides information on cardiopulmonary comorbidities. Four patients (approx. 17%) in the placebo arm had coronary heart disease, a condition for which, according to the summary of product characteristics (SmPC) for epoprostenol, extreme caution is advised, and were not treated with epoprostenol. However, the presented data do not reveal the drug combinations that were used for the treatment of these patients.

According to the notes of the G-BA, physiotherapeutic measures should be made available in both study arms. In its comments, the company provides information for patients in WHO FC IV. Accordingly, a total of 2 vs. 2 patients (10% vs. 8%) participated in a cardiopulmonary exercise programme. Such training was not recommended for 13 versus 14 patients (65% versus 58%). 3 vs. 8 patients (15% vs. 33%) did not participate in an exercise programme due to a lack of local availability, whilst 2 vs. 0 patients (10% vs. 0%) decided against it. Based on the available information, it is unclear to what extent other physiotherapeutic measures (e.g.

physiotherapy, exercise treatment, respiratory therapy) were available to patients in the study.

Overall, the data subsequently submitted in the company's comments and the information provided in the G-BA's commission reduced the uncertainties described in dossier assessment A26-12 regarding the implementation of the ACT specified by the G-BA in the ZENITH study. Information is now available on the drug combinations used in background therapy, as well as on the reasons for not using triple therapy. However, there remain uncertainties as to the extent to which treatment with the drug combination specified by the G-BA was not used due to a lack of availability or eligibility for reimbursement. Therefore, it cannot simply be assumed that the inclusion criterion relating to the comparator intervention (comparator group of the study) is met to at least 80%. Information on a possible effect modification due to a background therapy that does not correspond to the ACT specified by the G-BA (in particular, combination therapy without parenteral PCA) is available only for the total population. The subgroup analyses for the characteristic parenteral PCA therapy (yes vs. no; referred to in the study documents as 'Prostacyclin Infusion Therapy: prostacyclin infusion vs. non-prostacyclin infusion') for the primary outcome of the ZENITH study show that there is no significant effect modification by this characteristic in the total study population and that there is a significant advantage of sotatercept over placebo in both subgroups [7]. However, there are no corresponding analyses for the relevant subpopulation with WHO FC IV.

In this unusual data situation, the remaining uncertainties regarding the implementation of the ACT defined by the G-BA did not entirely call the observed effects into question. Despite the small analysis population, there are clear effects (see Section 2.3). In this specific data situation, the ZENITH study is therefore used for the benefit assessment within the framework of this addendum. On the one hand, the remaining uncertainties mean that at most hints can be derived and, on the other hand, that the extent of the observed effects cannot be quantified.

2.2 Study characteristics

The study presented in the following Table 2 was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study	Study category			Available sources		
	Study for the marketing authorisation of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
A011-14 (ZENITH[c])	Yes	Yes	No	Yes [2,3]	Yes [4-6]	Yes [7]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The detailed characteristics of the ZENITH study, including information on study design, intervention and study population can be found in dossier assessment A26-12.

As part of the commenting procedure, the company presented the results of the largely completely processed final analysis. Due to the clearly longer treatment and observation periods in the final analysis, the results of the final analysis are used for the benefit assessment within this addendum.

Information on the course of the study

Table 3 shows patients' median and mean treatment durations and the median and mean observation periods for individual outcomes.

Table 3: Information on the course of the study (subpopulation with WHO FC IV) – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study **duration of the study phase** **outcome category /** **outcome**	**Sotatercept + background therapy** **N = 20**	**Placebo + background therapy** **N = 24**
ZENITH (2nd data cut from 6 June 2025)		
Treatment duration [weeks]		
Median [Q1; Q3]	64.5 [44.4; 90.2]	37.4 [28.5; 57.2]
Mean (SD)	64.7 (35.3)	43.8 (24.2)
Observation period [weeks]		
Overall survival (main analysis)[a]		
Median [Q1; Q3]	72.9 [50.9; 96.6]	37.6 [27.4; 58.9]
Mean (SD)	70.8 (36.2)	44.2 (24.5)
Overall survival (sensitivity analysis)[a]		
Median [Q1; Q3]	77.9 [55.4; 107.3]	62.4 [49.9; 80.9]
Mean (SD)	78.7 (32.6)	62.8 (27.5)
Morbidity		
Disease worsening	ND[b]	ND[b]
Walking ability (6MWT)		
Median [Q1; Q3]	64.7 [24.1; 88.6]	36.1 [24.1; 58.9]
Mean (SD)	60.0 (39.0)	42.1 (26.0)
Dyspnoea (Borg CR10 scale)		
Median [Q1; Q3]	64.7 [24.1; 79.1]	36.1 [24.1; 58.9]
Mean (SD)	56.7 (34.9)	42.1 (26.0)
Health status (EQ-5D VAS)	N = 19	N = 21
Median [Q1; Q3]	67.4 [37.9; 73.3]	37.0 [24.4; 48.1]
Mean (SD)	61.9 (29.9)	41.3 (27.8)
Health-related quality of life	Outcome category not recorded	
Side effects		
Median [Q1; Q3]	68.3 [44.9; 90.4]	37.6 [27.4; 58.9]
Mean (SD)	65.8 (35.7)	44.0 (24.7)

a. The observation period was calculated based on the observed time to event/censoring/end of study of all patients (deceased and non-deceased). Primary analysis: excluding events that occurred following lung transplant or transition to the SOTERIA extension study; sensitivity analysis: including events that occurred following lung transplant or transition to the SOTERIA extension study

b. According to the company, the observation period for this outcome is the same as that for overall survival. This applies to the component death from any cause, whilst the components lung transplant and hospitalization for ≥ 24 hours due to worsening PAH were only recorded up to the end of the study (18 February 2025) and not up to the final data cut (6 June 2025). Information on the duration of follow-up for these components is not available.

6MWT: 6-minute walk test; CR10: 10-point category ratio scale; FC: functional class; ND: no data; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

For patients of the relevant subpopulation, the median and mean treatment durations and observation periods are clearly longer in the intervention arm than in the comparator arm. This is because the ZENITH study provided for a continuation of treatment until the occurrence of an event in the primary composite outcome (death from any cause, lung transplant or hospitalization for ≥ 24 hours due to worsening PAH), and follow-up ended shortly after the end of treatment. Follow-up was continued after the event of a lung transplant or hospitalization for ≥ 24 hours due to worsening PAH only for the sensitivity analysis on overall survival. Accordingly, the observation periods of the two arms do not differ so clearly for this analysis.

2.2.1 Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
ZENITH	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was assessed as low for the ZENITH study.

2.2.2 Transferability of the study results to the German health care context

According to the company, the ZENITH study results can be transferred to the German health care context due to the characteristics of the investigated patient population, the study design, and the on-label use of sotatercept.

It explains that the initial procedure on sotatercept had already demonstrated that parenteral prostacyclins are already routinely used in patients with WHO FC III. Accordingly, it could be assumed that, upon progression to WHO FC IV, a relevant proportion of patients were already receiving parenteral therapy with prostacyclins. For these patients, it was often no longer possible to escalate treatment, as all pathways had been exhausted and dose escalations were often no longer an option either. Consequently, continuation of the background therapy in combination with a placebo was consistent with the German health care context prior to the marketing authorization of sotatercept for WHO FC IV PAH and therefore constituted the adequate implementation of the ACT for these patients.

The company also points out that the study was chiefly conducted in countries with a health care system comparable to the German one. According to the company, results can therefore be transferred to the German health care context even for outcomes that can only be measured without bias in a comparable health care setting.

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

For the transferability to the German health care context, see also Section 2.1.

2.3 Results on added benefit

2.3.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - disease worsening
  - walking ability, recorded using the 6-minute walk test (6MWT)
  - dyspnoea, recorded using the Borg 10-point category ratio scale (CR10)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4).

Table 5 shows for which outcomes data were available in the included study.

Table 5: Matrix of outcomes – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study	Outcomes								
	Overall survival	Worsening of the disease[a]	Walking ability (6MWT)	Dyspnoea (Borg CR10 scale)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs
ZENITH	Yes	Yes	Yes	Yes	Yes	No[b]	Yes	Yes	No[c]

a. Composite outcome comprising the components death from any cause, lung transplant and hospitalization for ≥ 24 hours due to worsening PAH.
b. Outcomes in this category were not recorded.
c. No specific AEs identified based on the AEs occurring in the relevant study.

6MWT: 6-minute walk test; AE: adverse event; CR10: 10-point category ratio scale; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on outcomes

Overall survival

As described in dossier assessment A26-12, the study documents of the ZENITH study define various analyses of overall survival:

- Main analysis: death from any cause up to the data cut, excluding events that occurred following lung transplant or transition to the SOTERIA extension study.
- Sensitivity analysis: death from any cause up to the data cut, including events that occurred following lung transplant or transition to the SOTERIA extension study.

In this data situation, both analyses are subject to uncertainties (see Section 2.3.2). The main analysis does not consider events that occur after lung transplant or transition to the SOTERIA extension study. The sensitivity analysis takes all events into account; however, patients in the comparator arm of the ZENITH study who received sotatercept in the SOTERIA extension study continued to be treated as patients in the placebo arm. In this data situation, both analyses are considered together and used to derive the added benefit.

Disease worsening

The primary composite outcome of the ZENITH study was operationalized as death from any cause, lung transplant or hospitalization for ≥ 24 hours due to worsening PAH (adjudicated by a blinded committee). All three individual components of the outcome are considered to be relevant to patients. In this population with a high risk of mortality, hospitalization for ≥ 24 hours due to worsening PAH is a potentially life-threatening event. The same applies to a lung transplant.

The evaluations of the main analysis of the primary outcome of the ZENITH study presented by the company were used to operationalize the outcome disease progression.

Walking ability (6MWT)

The company conducted responder analyses of time to first improvement for the outcome of walking ability recorded using the 6MWT. In this context, the company used the post hoc specified response criteria of ≥ 40 m and ≥ 33 m. For the 6MWT, no response threshold was established in the present indication of PAH [11-14]. Furthermore, the response criteria ≥ 40 m and ≥ 33 m had not been predefined. Moreover, the company presented an analysis of the median difference between the treatment arms at Week 24 compared with baseline for the outcome walking ability, recorded with the 6MWT (Hodges-Lehman Location Shift). The time points of recording between the start of the study and Week 24 (Weeks 3 and 12) were not considered in this analysis. This is the prespecified analysis of the outcome in the ZENITH study. This addendum presents the prespecified analysis of the median difference between the treatment arms at Week 24.

2.3.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study	Study level	Outcomes								
		Overall survival	Worsening of the disease[a]	Walking ability (6MWT)	Dyspnoea (Borg CR10 scale)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Specific AEs
ZENITH	L	H[b]	L	H[c, d]	H[d]	H[d]	–[e]	H[f]	L[g]	–[h]

a. Composite outcome comprising the components death from any cause, lung transplant and hospitalization for ≥ 24 hours due to worsening PAH.
b. For reasons, see running text below.
c. High proportion of patients with missing values that may not have been adequately imputed.
d. Incomplete observations for potentially informative reasons.
e. Outcomes in this category were not recorded.
f. It is assumed that disease-related events were also included in the outcome (for the reasoning, see text below).
g. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be limited (for reasons, see running text below).
h. No specific AEs were identified based on the AEs occurring in the relevant study.

6MWT: 6-minute walk test; AE: adverse event; CR10: 10-point category ratio scale; H. high; L: low; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

For the main analysis of overall survival, there is a high outcome-specific risk of bias due to incomplete observations for potentially informative reasons, as events that occurred following lung transplant or following hospitalization for ≥ 24 hours due to worsening PAH were not included but censored.

There is a high outcome-specific risk of bias in the sensitivity analysis of overall survival, as patients in the comparator arm were also treated with sotatercept during the observation period following their transition to the SOTERIA extension study, which may potentially bias the effect. This applies in particular to the 9 patients (38%, Institute's calculation) in the comparator arm who had transitioned to the SOTERIA extension study following hospitalization and for whom potentially long treatment durations with sotatercept were thus considered in the analysis. To a lesser extent, this also applies to the 8 patients (33%) in the comparator arm who transitioned to the SOTERIA extension study due to the end of the

ZENITH study and were followed-up while being treated with sotatercept until the final data cut.

There is a high outcome-specific risk of bias for walking ability (6MWT) and for the patient-reported outcomes dyspnoea (Borg CR10 scale) and health status (EQ-5D VAS), as there is incomplete observation for potentially informative reasons. The reason for this is that these outcomes were only recorded for the duration of treatment with the study medication (plus 3 weeks or 8 weeks, respectively) and that events in the primary outcome entailed the discontinuation of treatment with the study medication and, consequently, the end of the follow-up period. For the patient-reported outcomes, there was a differential decrease of the response rates to the respective questionnaire over the course of the study. With regard to walking ability (6MWT), there is also a high proportion of patients with missing values at Week 24, which may not have been adequately imputed.

For the outcome SAEs, there is a high outcome-specific risk of bias, as the available data suggest that high proportions of potentially disease-related events (in particular SAEs of the SOC respiratory, thoracic and mediastinal disorders, thoracic cavity and mediastinum'; see Table 14) were included in the analyses presented.

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

2.3.3 Results

Table 7 and Table 8 summarize the results of the comparison of sotatercept with placebo in adults with WHO FC IV PAH. Where necessary, the data provided by the company are supplemented with calculations conducted by the Institute.

Table 7: Results (mortality, morbidity, side effects, time to event; subpopulation with WHO FC IV) – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy (multipage table)

Study outcome category outcome	Sotatercept + background therapy		Placebo + background therapy		Sotatercept + background therapy vs. placebo + background therapy
	N	median time to event[a] [95% CI] patients with event n (%)	N	median time to event[a] [95% CI] patients with event n (%)	HR [95% CI]; p-value[b]
ZENITH (2nd data cut from 6 June 2025)					
Mortality					
Overall survival					
Main analysis[c]	20	NA [25.4; NC] 3 (15.0)	24	NA 3 (12.5)	0.68 [0.11; 4.19]; 0.679
Sensitivity analysis[c]	20	NA [25.4; NC] 4 (20.0)	24	NA 5 (20.8)	0.78 [0.20; 3.00]; 0.717
Morbidity					
Worsening of the disease[d]	20	NA [25.4; NC] 5 (25.0)	24	9.5 [5.3; NC] 14 (58.3)	0.25 [0.08; 0.78]; 0.017
Death from any cause	20	3 (15.0)	24	0 (0.0)	
Lung transplant	20	1 (5.0)	24	0 (0.0)	
Hospitalization for ≥ 24 hours due to worsening PAH	20	1 (5.0)	24	14 (58.3)	
Dyspnoea (Borg CR10 scale – time to first improvement[e])	20[f]	24.1 [12.1; NC] 12 (60.0)	24[f]	NA [24.1; NC] 9 (37.5)	2.04 [0.86; 4.85]; 0.107
Health status (EQ-5D VAS - time to first improvement[g])	18[f]	24.2 [12.1; 49.1] 13 (72.2)	22[f]	NA [12.3; NC] 7 (31.8)	2.04 [0.81; 5.16]; 0.130
Health-related quality of life					
Outcome category not recorded					
Side effects					
AEs (supplementary information)	20	0.9 [0.1; 3.1] 19 (95.0)	24	5.2 [2.3; 9.1] 23 (95.8)	–
SAEs[h]	20	46.4 [10.3; NC] 12 (60.0)	24	23.1 [11.9; 55.0] 17 (70.8)	0.71 [0.34; 1.49]; 0.365
Discontinuation due to AEs	20	NA 0 (0)	24	NA 1 (4.2)	NC; 0.374

Table 7: Results (mortality, morbidity, side effects, time to event; subpopulation with WHO FC IV) – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy (multipage table)

Study outcome category outcome	Sotatercept + background therapy		Placebo + background therapy		Sotatercept + background therapy vs. placebo + background therapy
	N	median time to event[a] [95% CI] patients with event n (%)	N	median time to event[a] [95% CI] patients with event n (%)	HR [95% CI]; p-value[b]

a. The median time to event is shown in months for the outcomes overall survival and disease worsening, and in weeks for the outcomes dyspnoea (Borg CR10 scale) and health status (EQ-5D VAS), as well as for the outcomes in the side effects category.
b. HR and CI: Cox proportional hazards model, p-value: Wald test, score test in case of zero events in one of the study arms.
C. Main analysis: excluding events that occurred following lung transplant or transition to the SOTERIA extension study; sensitivity analysis: including events that occurred following lung transplant or transition to the SOTERIA extension study
d. Composite outcome comprising the components death from any cause, lung transplant and hospitalization for ≥ 24 hours due to worsening PAH; following review by an independent, blinded adjudication committee.
e. A decrease by ≥ 1.5 points from baseline is considered a clinically relevant improvement (scale range: 0 to 10).
f. Number of patients with values at baseline and at least one later time point.
g. An increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100).
h. It is assumed that disease-related events were also included in the outcome (for the reasoning, see Section 2.3.2).

6MWT: 6-minute walk test; AE: adverse event; CI: confidence interval; CR10: 10-point category ratio scale; FC: functional class; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; Q1: 1st quartile; Q3: 3rd quartile; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

Table 8: Results (morbidity, continuous) – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study outcome category outcome	Sotatercept + background therapy			Placebo + background therapy			Sotatercept + background therapy vs. placebo + background therapy
	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
ZENITH (2nd data cut from 6 June 2025)							
Morbidity							
Walking ability (6MWT) at Week 24	20	197.5 [122.9; 306.1]	91.5 [78.8; 95.5]	24	237.5 [173.5; 327.0]	−5.0 [−5.0; −5.0]	86.24 [−7.84; 180.31]; 0.059

a. Number of patients taken into account in the effect estimation; baseline values (and values at Week 24) may be based on different patient numbers. For patients with missing value at Week 24 due to death, the worst rank value compared with baseline was imputed. For patients with missing value at Week 24 due to a nonfatal event in the primary outcome, the next-worst rank value compared with baseline was imputed. Multiple imputation was used for patients with missing value at Week 24 due to other reasons. Overall, imputed values were used for 4 (20%) versus 5 (21%) of the patients (Institute's calculation).
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 walk 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

Based on the available information, at most hints, e.g. of an added benefit, could be determined for all outcomes (for reasoning, see Section 2.1).

Mortality

In both analyses used, there was no statistically significant difference between the treatment groups for the outcome overall survival. There is no hint of an added benefit of sotatercept in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Disease worsening

For the outcome disease worsening, operationalized as death from any cause, lung transplant or hospitalization for ≥ 24 hours due to worsening PAH, there was a statistically significant difference in favour of sotatercept over placebo. This resulted in a hint of added benefit of sotatercept in comparison with the ACT.

Walking ability (6MWT)

For the outcome walking ability (recorded using the SF-6MWT), no statistically significant difference between treatment groups was found. There is no hint of an added benefit of sotatercept in comparison with the ACT; an added benefit is therefore not proven.

Dyspnoea (Borg CR10 scale)

No statistically significant difference between treatment groups was found for the outcome dyspnoea (recorded using the Borg CR10 scale). However, there was an effect modification by the characteristic Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2.0 risk score. For patients with a baseline REVEAL Lite 2.0 risk score of 9 to 10, there is no hint of an added benefit of sotatercept compared with the ACT; therefore, no added benefit was proven for patients with a baseline REVEAL Lite 2.0 risk score of 9 to 10. For patients with a baseline REVEAL Lite 2.0 score of ≥ 11, however, there was a hint of an added benefit of sotatercept over the ACT.

Health status (EQ-5D VAS)

No statistically significant difference between treatment groups was found for the outcome of health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of sotatercept in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

Outcomes in the category of health-related quality of life were not recorded in the ZENITH study.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes SAEs or discontinuation due to AEs. In each case, there is no hint of an added benefit of sotatercept in comparison with the ACT; an added benefit is therefore not proven.

2.3.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (<65 years versus ≥65 years)
- Sex (male versus female)
- REVEAL Lite 2.0 risk score (9 to 10 vs. ≥ 11)

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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 9. The Kaplan-Meier curves on the subgroup results are presented in Appendix A.2.

Table 9: Subgroups (mortality, time to event, subpopulation with WHO-FK IV) – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study outcome characteristic subgroup	Sotatercept + background therapy		Placebo + background therapy		Sotatercept + background therapy vs. placebo + background therapy	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95% CI][a]	p-value[a]
ZENITH						
Dyspnoea (Borg CR10 scale – time to first improvement[b])						
REVEAL Lite 2.0 risk score						
9 to 10	8	NA [0.7; NC] 3 (37.5)	15	9.0 [3.0; NC] 7 (46.7)	0.70 [0.18; 2.72]	0.605
≥ 11	12	2.8 [2.8; 5.6] 9 (75.0)	9	NA [2.8; NC] 2 (22.2)	6.69 [1.38; 32.38]	0.018
Total					Interaction:	0.023[c]

a. HR and CI: Cox proportional hazards model; p-value: Wald test.
b. A decrease by ≥1.5 points from baseline is considered a clinically relevant improvement (scale range: 0 to 10).
c. p-value for the interaction between treatment and subgroup factor.

CI: confidence interval; CR10: 10-point category ratio scale; FC: functional class; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; REVEAL: Registry to Evaluate Early and Long-Term PAH Disease Management

Morbidity

Dyspnoea (Borg CR10 scale)

For the outcome dyspnoea (assessed using the Borg CR10 scale), there is an effect modification by the characteristic REVEAL Lite 2.0 risk score. For patients with a baseline REVEAL Lite 2.0 risk score of 9 to 10, there is no statistically significant difference between the treatment groups. There is no hint of an added benefit of sotatercept in comparison with the ACT for this patient group; an added benefit is therefore not proven.

For patients with a baseline REVEAL Lite 2.0 risk score of ≥ 11, however, a statistically significant difference was found in favour of sotatercept over the ACT. There was a hint of added benefit of sotatercept in comparison with the ACT for this patient group.

2.4 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [15].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.1 Assessment of added benefit at outcome level

Determination of the outcome category for symptom outcomes

For the symptom outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Disease worsening

Disease worsening is operationalized as death from any cause, lung transplant or hospitalization for ≥ 24 hours due to worsening PAH. As described in Section 2.3.1, the component hospitalization for ≥ 24 hours due to worsening PAH is a potentially life-threatening event in this population with a high risk of mortality. The same applies to a lung transplant. As both components are therefore considered to be sufficiently similar to death in terms of their severity, the outcome disease worsening is altogether classified as serious/severe.

Dyspnoea (Borg CR10 scale)

The Borg CR10 scale ranges from 0 to 10 (0: ‘no dyspnoea at all’, 10: ‘extreme dyspnoea’). Patients in the entire subpopulation with WHO FC IV have an average baseline score of around 5, which corresponds to severe dyspnoea (mean [standard deviation]: 5.8 [4.3] vs. 4.3 [3.5]). The company did not provide any information on baseline values for the subgroup of patients with a REVEAL Lite 2.0 risk score of ≥ 11. However, as these patients had a higher disease severity, it is assumed that they had at least severe dyspnoea. Consequently, the outcome dyspnoea is classified as serious/severe for these patients.

Table 10: Extent of added benefit at outcome level: sotatercept + background therapy vs. placebo + background therapy (subpopulation with WHO FC IV) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Sotatercept + background therapy vs. placebo + background therapy** **median time to event or median change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival Main analysis[c]	NA vs. NA HR: 0.68 [0.11; 4.19]; p=0.679	Lesser benefit not proven / added benefit not proven
Sensitivity analysis[c]	NA vs. NA HR: 0.78 [0.20; 3.00]; p=0.717	
Morbidity		
Disease worsening	NA vs. 9.5 months HR: 0.25 [0.08; 0.78]; p=0.017 probability: hint	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
Walking ability (6MWT) at Week 24	91.5 m vs. −5.0 m HLLS: 86.24 [-7.84; 180.31]; p=0.059	Lesser benefit not proven / added benefit not proven
Dyspnoea (Borg CR10 scale – time to first improvement) REVEAL Lite 2.0 risk score 9 to 10	NA vs. 9.0 months 0.70 [0.18; 2.72]; p=0.605	Lesser benefit not proven / added benefit not proven
≥ 11	2.8 months vs. NA HR: 6.69 [1.38; 32.38]; HR: 0.15 [0.03; 0.72]d; p=0.018 probability: hint	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health status (EQ-5D VAS - time to first improvement)	24.2 weeks vs. NA. HR: 2.04 [0.81; 5.16]; p=0.130	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
	Outcome category not recorded	

Table 10: Extent of added benefit at outcome level: sotatercept + background therapy vs. placebo + background therapy (subpopulation with WHO FC IV) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Sotatercept + background therapy vs. placebo + background therapy** **median time to event or median change** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	46.4 vs. 23.1 weeks HR: 0.71 [0.34; 1.49]; p=0.365	Lesser benefit not proven / added benefit not proven
Discontinuation due to AEs	NA vs. NA HR: NC; p=0.374	Lesser benefit not proven / added benefit not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Only events that occurred within a shortened recording period were included in the prespecified main analysis of overall survival (excluding events that occurred following lung transplant or transition to the SOTERIA extension study). The prespecified sensitivity analysis of overall survival (including events that occurred after lung transplant or transition to the SOTERIA extension study) includes events throughout the entire study duration.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

6MWT: 6-minute walk test; AE: adverse event; CR10: 10-point category ratio scale; FC: functional class; HLLS: Hodges-Lehman Location Shift; HR: hazard ratio; CI: confidence interval; CI_o: upper limit of the confidence interval; NA: not achieved; NC: not calculable; PAH: pulmonary arterial hypertension; REVEAL: Registry to Evaluate Early and Long-Term PAH Disease Management; SAE: serious adverse event; VAS: visual analogue scale

2.4.2 Overall conclusion on added benefit

Table 11 summarizes the results included in the overall conclusion on the extent of the added benefit.

Table 11: Positive and negative effects from the assessment of sotatercept + background therapy compared with placebo + background therapy (subpopulation WHO-FC IV)

Positive effects	**Negative effects**
Serious/severe symptoms / late complications ▪ disease worsening: hint of added benefit – extent: "non-quantifiable" ▪ dyspnoea (Borg CR10 scale) ▫ REVEAL Lite 2.0 risk score (≥ 11): hint of added benefit – extent: "non quantifiable"	–
Outcomes from the category health-related quality of life were not recorded.	
CR10: 10-point category ratio; FC: functional class; PAH: pulmonary arterial hypertension; REVEAL: Registry to Evaluate Early and Long-Term PAH Disease Management	

Overall, sotatercept has shown exclusively positive effects compared with the ACT.

The benefit in the case of disease worsening is decisive for the assessment. Furthermore, patients with a baseline REVEAL Lite 2.0 risk score of ≥ 11 showed a benefit in the outcome dyspnoea (assessed using the Borg CR10 scale). Due to the uncertainty described in Section 2.1 regarding the implementation of the ACT specified by the G-BA, at most hints can be derived, and moreover, the extent of added benefit cannot be quantified.

In summary, there is a hint of a non-quantifiable added benefit of sotatercept over the ACT for adults with WHO FC IV PAH.

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

2.5 Summary

The data subsequently submitted by the company in the commenting procedure alter the conclusion on the added benefit of sotatercept set out in dossier assessment A26-12. The company's comments and the information from the G-BA's commission reduced the uncertainties described in the dossier assessment regarding the implementation of the ACT specified by the G-BA in the ZENITH study. In this light and in this extraordinary data situation with pronounced effects, the remaining uncertainty regarding the implementation of the ACT defined by the G-BA did not entirely call the observed effects into question. In this specific data situation, the ZENITH study is therefore used for the benefit assessment within the framework of this addendum. However, the remaining uncertainty means that at most hints can be derived and, moreover, the extent of the added benefit cannot be quantified. In summary, there is a hint of a non-quantifiable added benefit of sotatercept over the ACT for adults with WHO FC IV PAH.

The following Table 12 shows the result of the benefit assessment of sotatercept, taking into account dossier assessment A26-12 and this addendum.

Table 12: Sotatercept – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with WHO FC IV PAH	Epoprostenol in combination with ERAs (ambrisentan, bosentan, macitentan) and PDE5is (sildenafil, tadalafil)[b, c]	Hint of a non-quantifiable added benefit

a. Presented is the ACT specified by the G-BA.
b. No drugs other than the PCA epoprostenol are approved for the treatment of patients with WHO FC IV PAH. According to the G-BA, the off-label use of a combination therapy with an ERA and PDE5I, in addition to the approved epoprostenol, is regarded as the therapy standard in the therapeutic indication under assessment and is generally to be preferred to monotherapy with drugs containing the active substance epoprostenol that have previously been approved for the therapeutic indication (Section 6(2), third sentence, point 2 of the AM-NutzenV).
c. Further comments from the G-BA:
- The guideline recommends a combination therapy comprising ERA, PDE5I and a PCA for the treatment of patients with WHO FC IV PAH. According to feedback from clinical experts, this treatment regimen currently represents the therapy standard for the majority of patients in the considered indication. Instead of parenteral epoprostenol, parenteral treprostinil may also be accepted as part of triple therapy (PCA + ERA + PDE5i). Where study participants receive combination therapy without parenteral PCA, the fact that these individuals are not suitable for treatment with parenteral PCA must be documented and discussed in the dossier of the benefit assessment.
- It is assumed that combination therapies are generally used in this therapeutic indication. Furthermore, it is assumed that all patients in both study arms will have access to the continuation of the treatment options approved for less serious WHO functional classes, or that these treatment options will be initiated in case of a corresponding indication. If, at the start of the study, further treatment escalation is not an option for patients, this must be documented and justified in the dossier.
- It is assumed that individualized concomitant medication (oxygen supply, diuretics, anticoagulants) is available in both study arms.
- In principle, a lung transplant or a heart-lung transplant is a treatment option for patients with WHO FC IV. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication.
- There are recommendations for non-drug physiotherapeutic measures to improve symptoms and exercise capacity. Physiotherapeutic measures in the sense of the Remedies Directive (physical therapy, e.g. physiotherapy, if indicated, should be made available to patients in both arms of the study in addition to drug therapy.

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

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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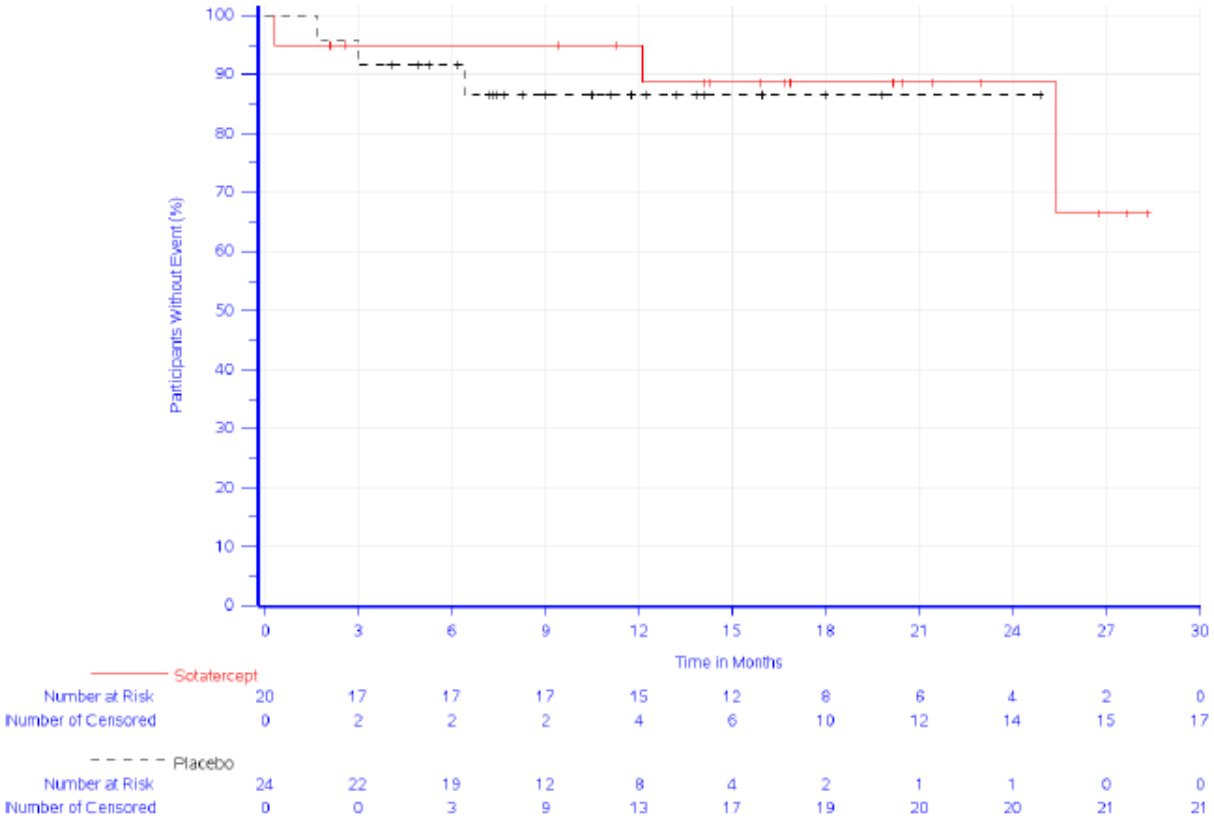
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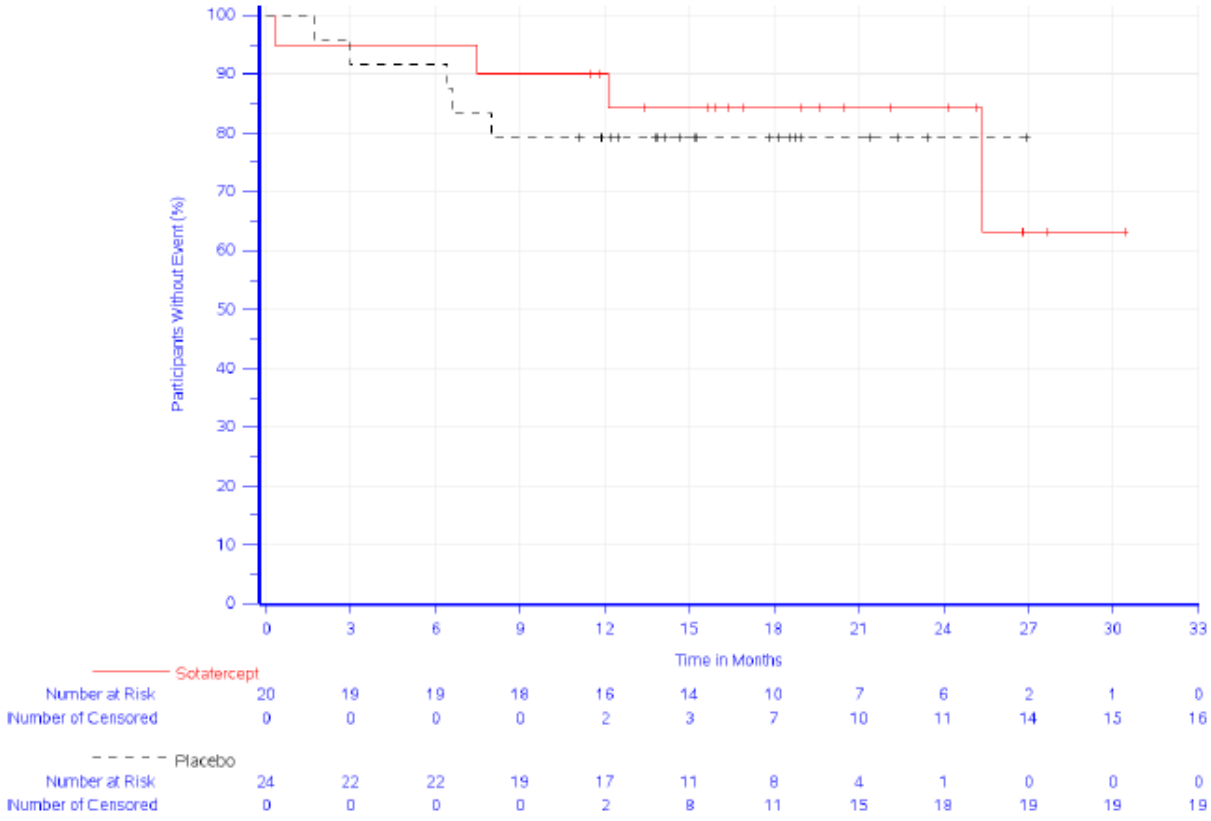
Appendix A Kaplan-Meier curves and graphs

A.1 Mortality



Study: ZENITH (MK-7962-006) (Database Cutoff Date: 06JUN2025)
Overall Survival
This figure includes all-cause deaths up to the study completion, except for those occurring after lung transplantation or enrollment in SOTERIA

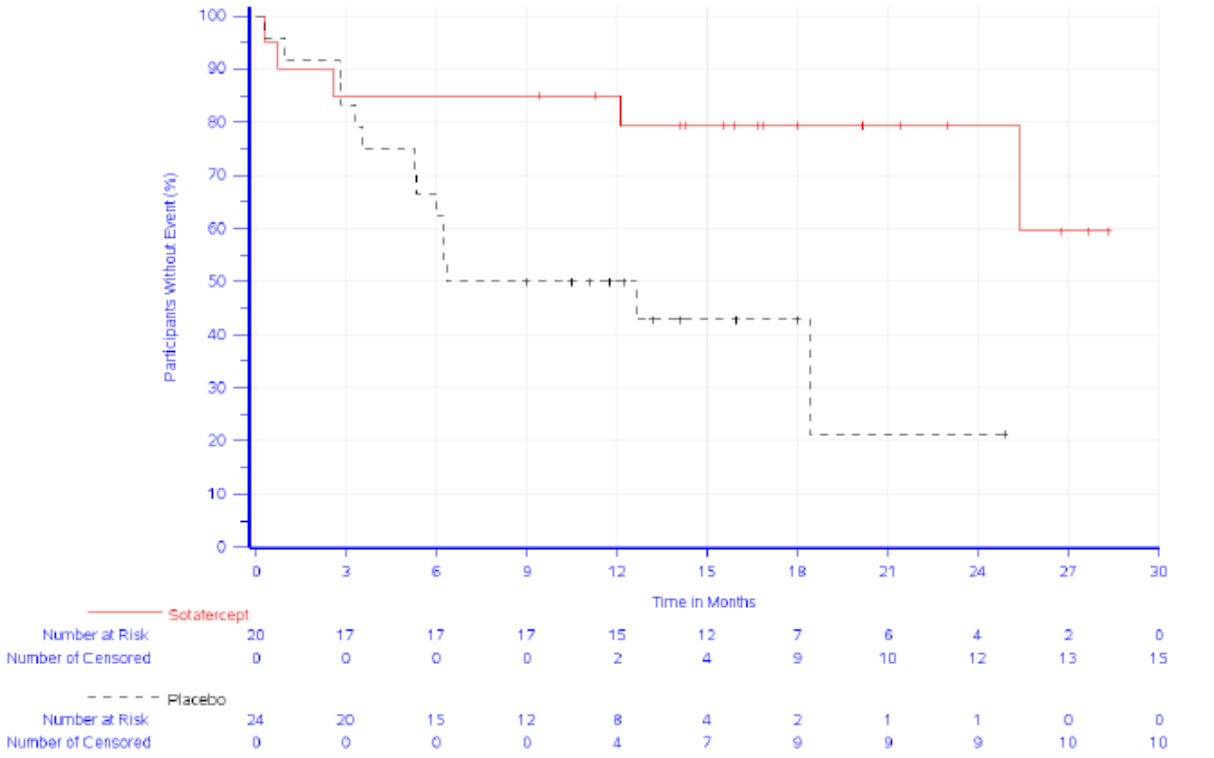
Figure 1: Kaplan-Meier curves for the outcome overall survival (main analysis) of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV



Study: ZENITH (MK-7962-006) (Database Cutoff Date: 06JUN2025)
Overall Survival (Sensitivity Analysis {\96} Include All Deaths)
This figure includes all-cause deaths up to the data cutoff date, including deaths after lung transplantation or after enrollment in SOTERIA

Figure 2: Kaplan-Meier curves for the outcome overall survival (sensitivity analysis) of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV

A.2 Morbidity



Study: ZENITH (MK-7962-006) (Database Cutoff Date: 06JUN2025)
All-cause Death, Lung Transplantation, or PAH Worsening-related Hospitalization of >= 24 Hours
This figure includes only the first adjudication-confirmed event of PAH worsening-related hospitalization >= 24 hours, lung transplantation, or all-cause death that occurred prior to the study completion date, excluding events that occurred in SOTERIA. For hospitalization and lung transplantation, events were only collected up to the individual participant's study completion date. Deaths are included regardless of adjudication

Figure 3: Kaplan-Meier curves for the outcome disease worsening (primary composite outcome comprising death from any cause, lung transplant or hospitalization for ≥ 24 hours due to worsening PAH) of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV

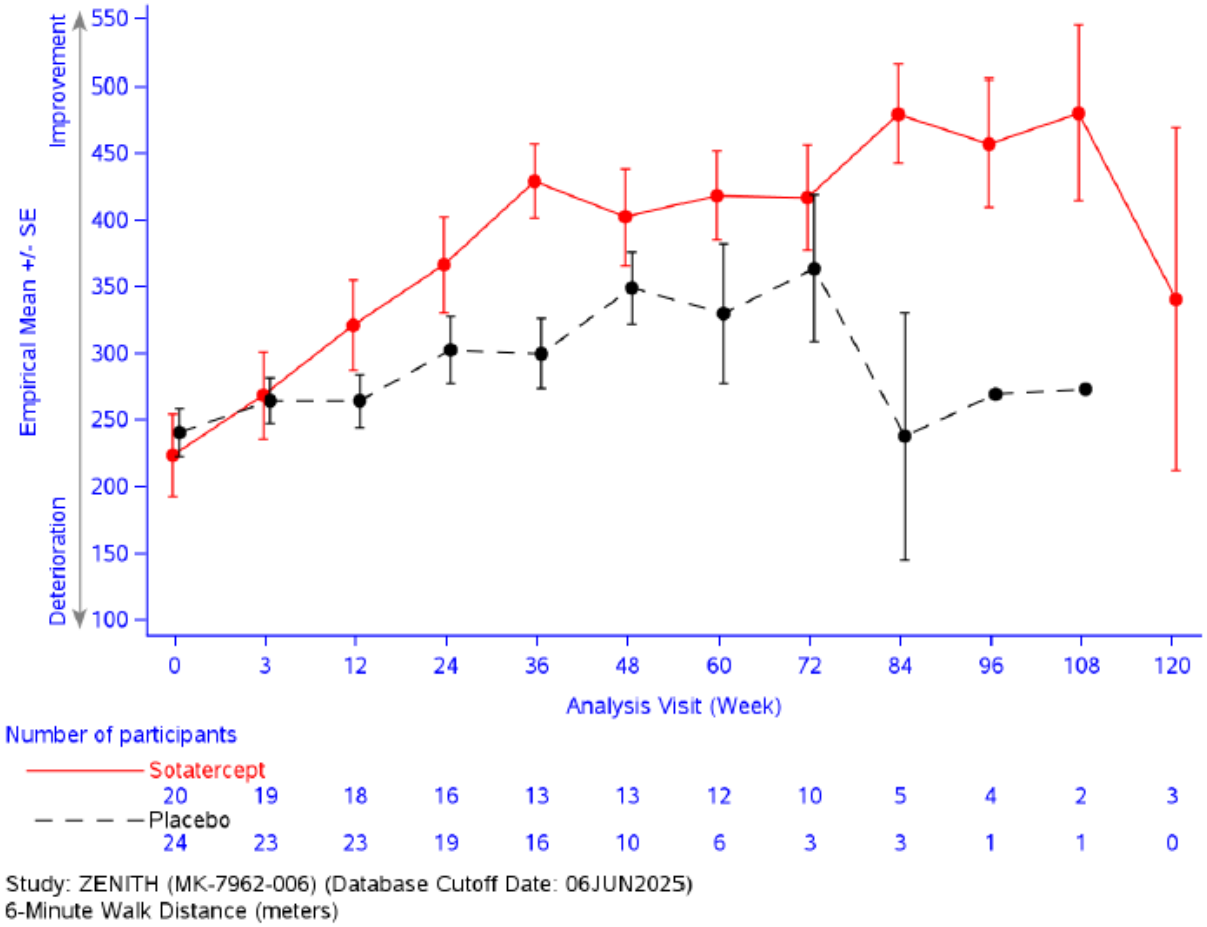


Figure 4: Curve for the outcome walking ability (6MWT) of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV

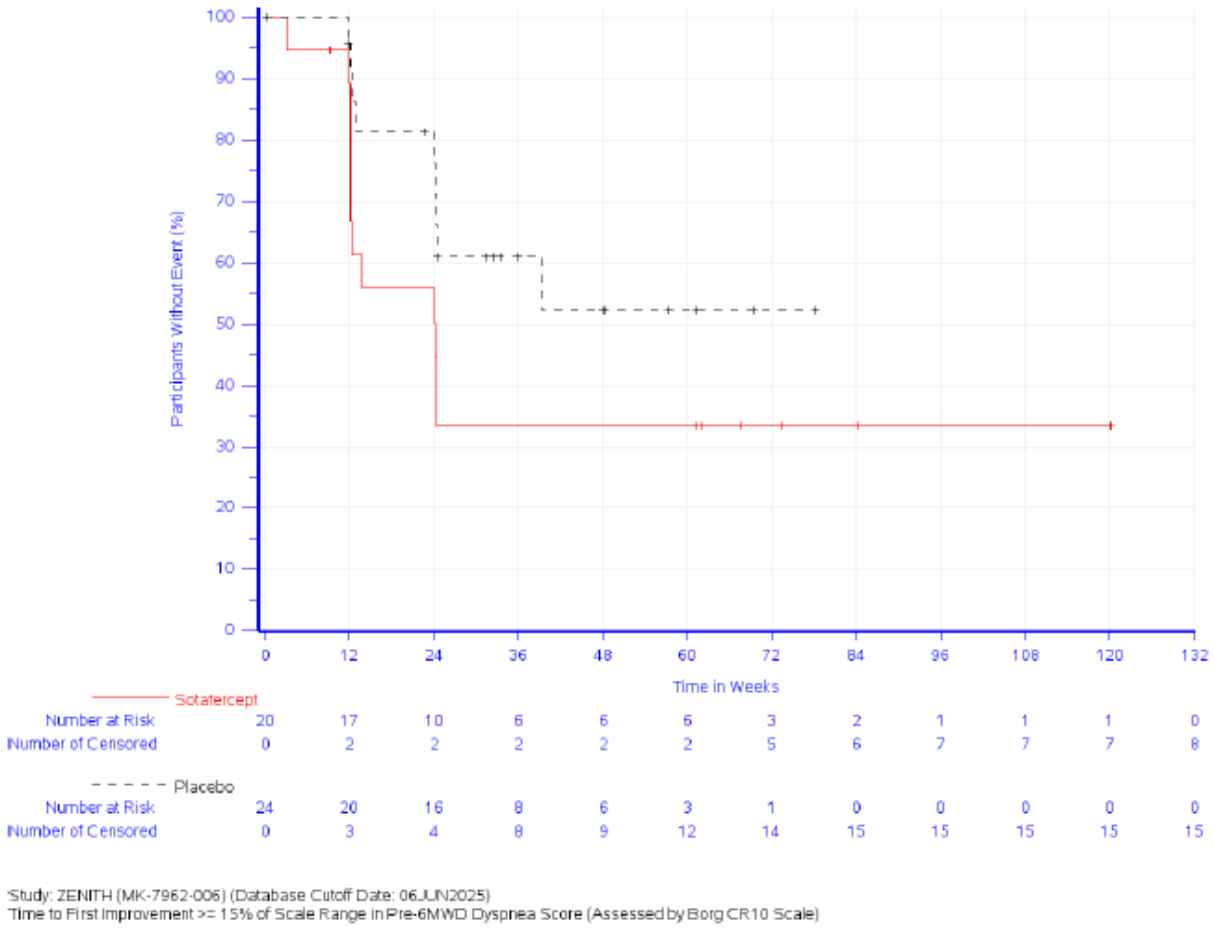


Figure 5: Kaplan-Meier curves for the outcome dyspnoea (Borg CR10 scale) of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV

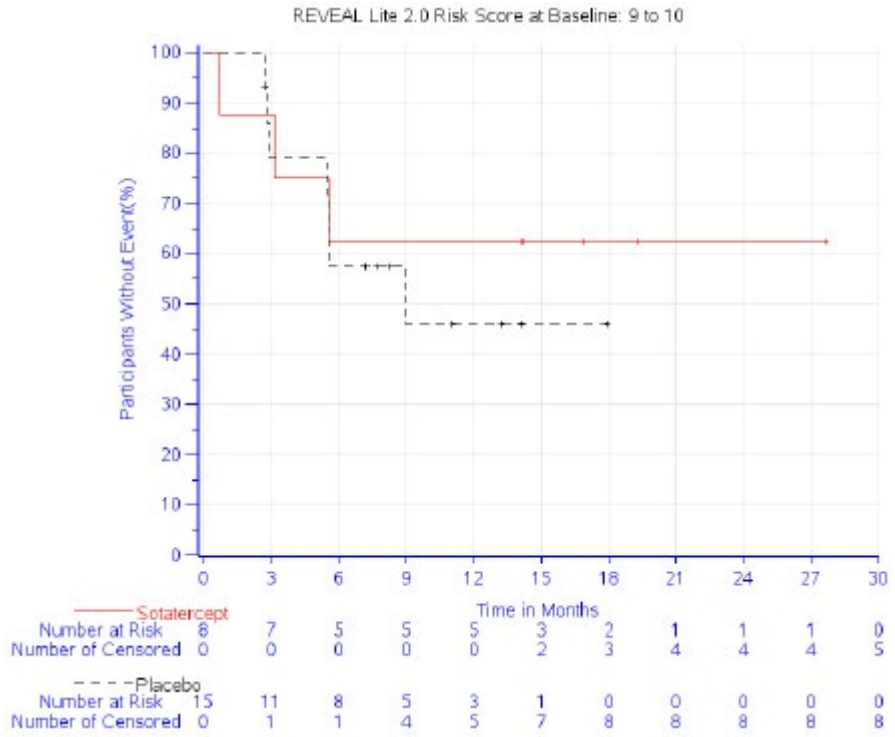


Figure 6: Kaplan-Meier curves for the outcome dyspnoea (Borg CR10 scale) from the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV, subgroup: REVEAL Lite 2.0 risk score 9 to 10

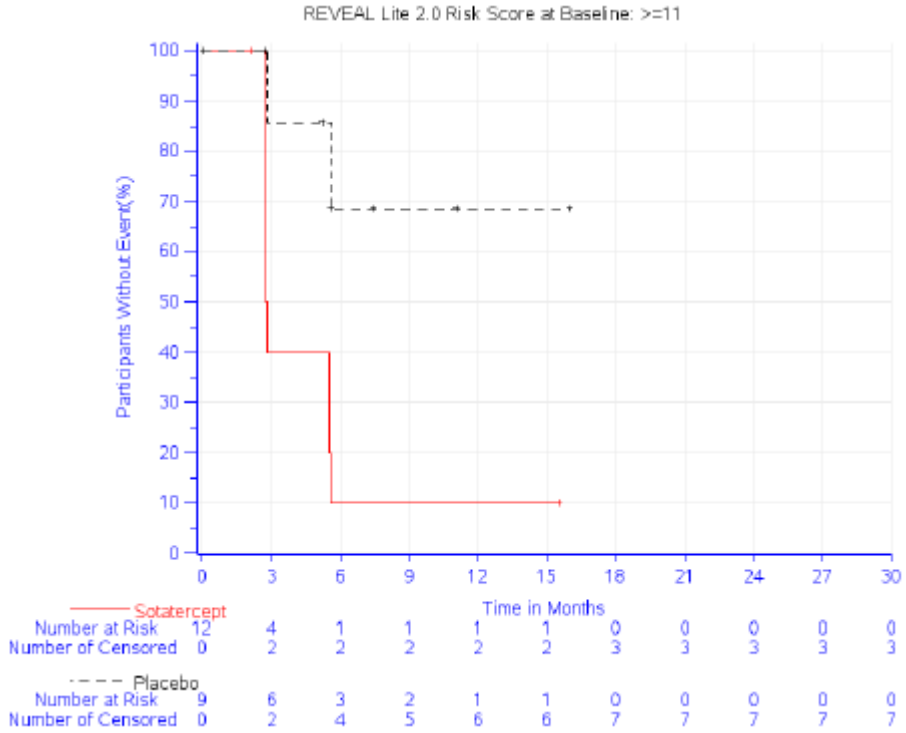


Figure 7: Kaplan-Meier curves for the outcome dyspnoea (Borg CR10 scale) of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV, subgroup: REVEAL Lite 2.0 risk score ≥ 11

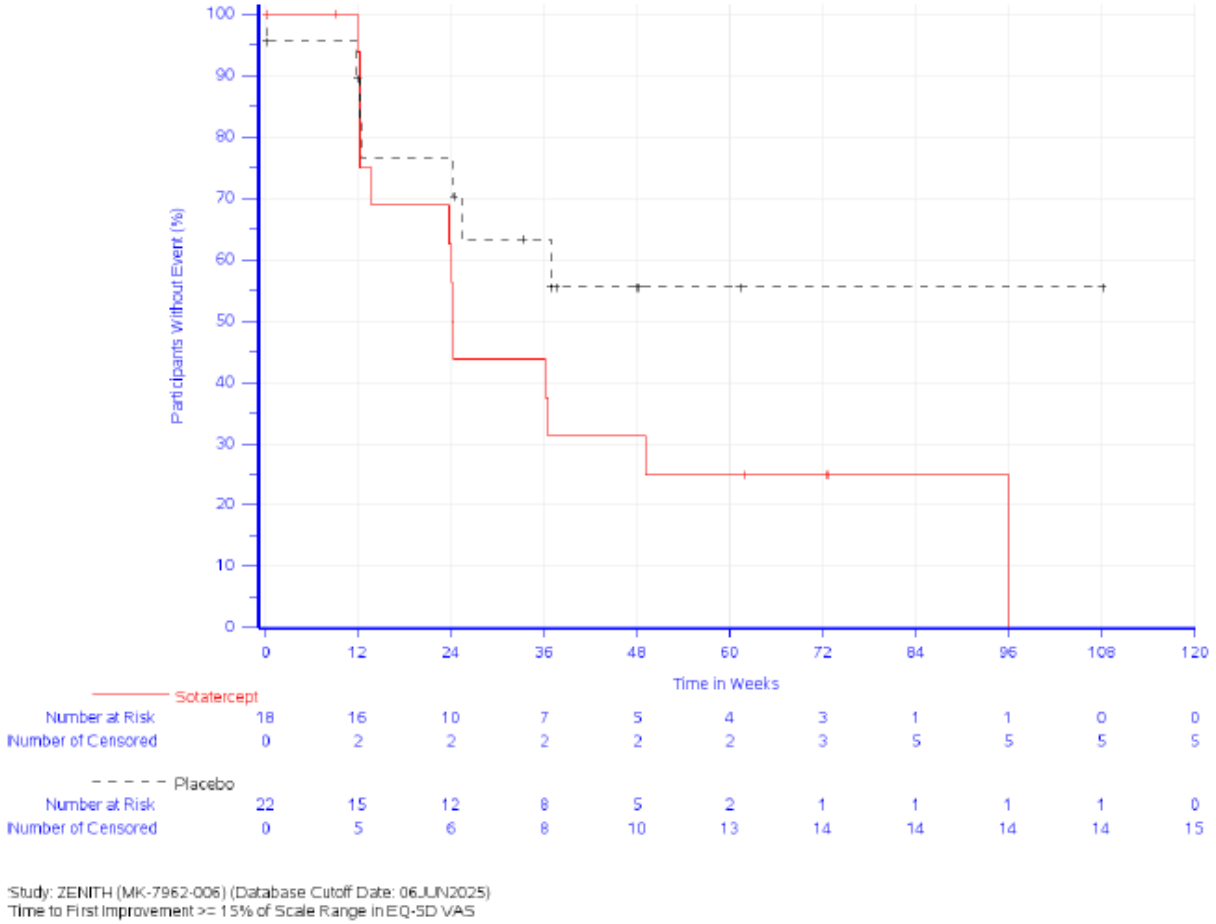


Figure 8: Kaplan-Meier curves for the outcome health status (EQ-5D VAS) of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV

A.3 Side effects

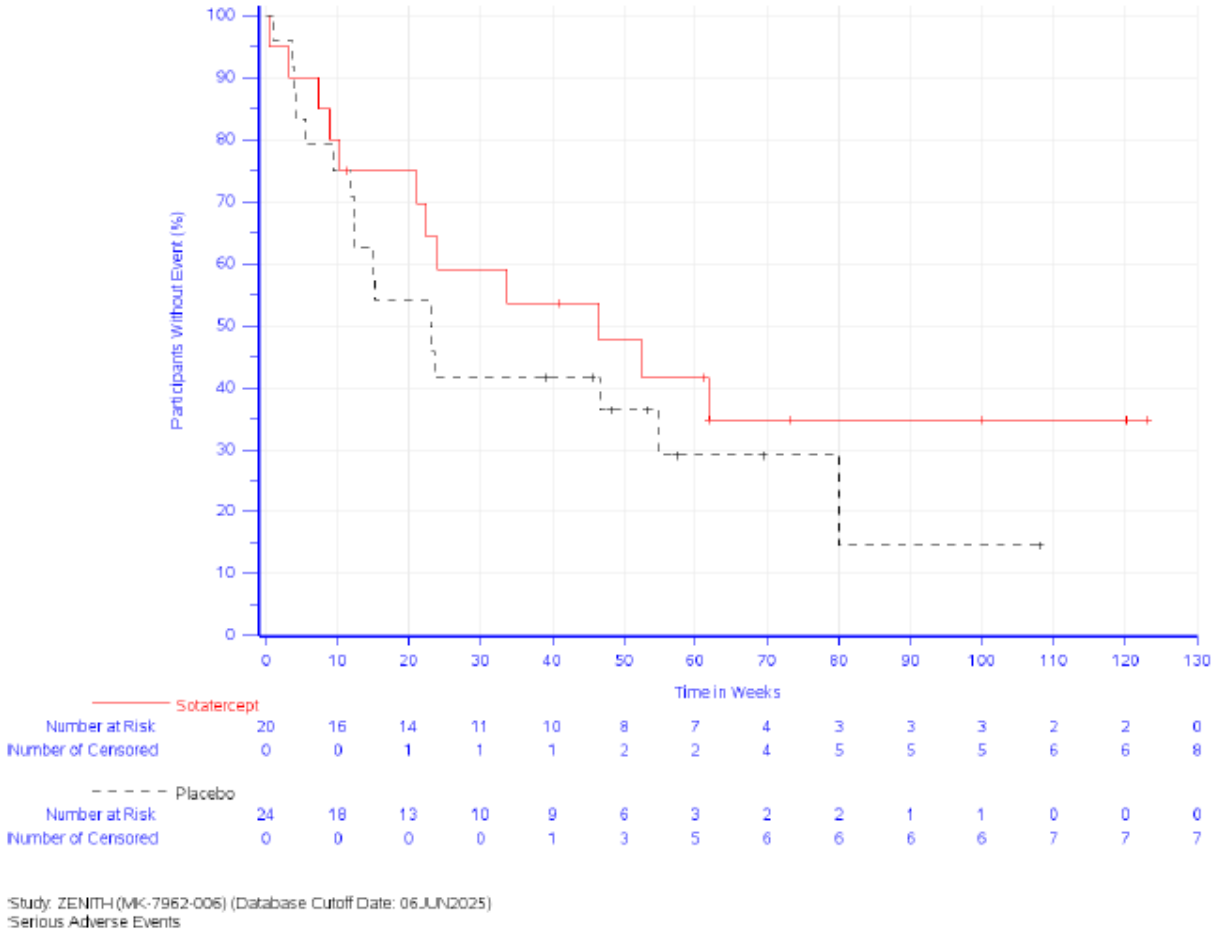


Figure 9: Kaplan-Meier curves for the outcome SAEs of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV

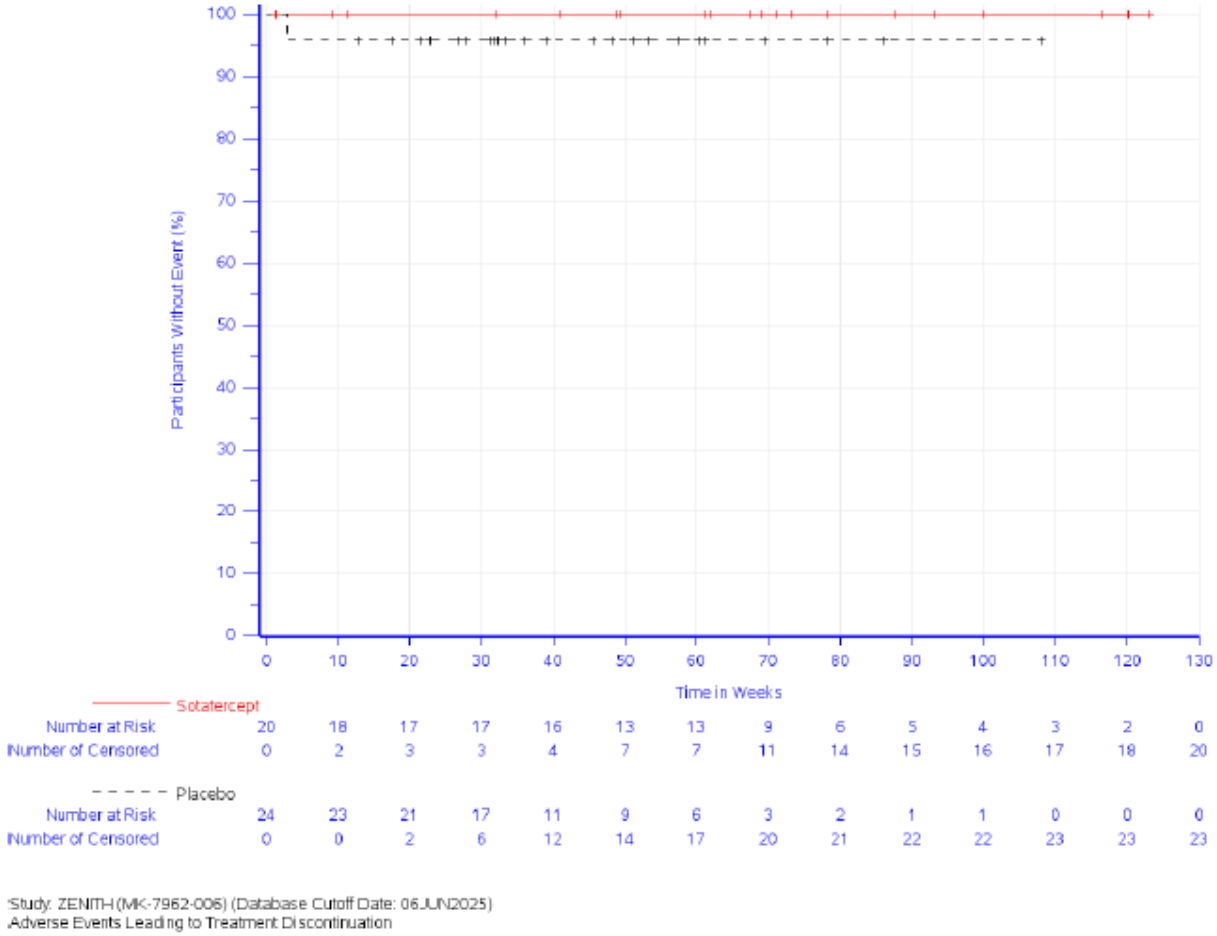


Figure 10: Kaplan-Meier curves for the outcome discontinuation due to AEs of the RCT ZENITH, 2nd data cut (6 June 2025), subpopulation with WHO FC IV

Appendix B Results on side effects

The tables below present proportions of events of the SOCs and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA) for AEs, SAEs, each on the basis of the following criteria:

- AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- SAEs: events that occurred in at least 5% of patients in one study arm
- Additionally, for all events irrespective of severity: 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, all events (SOCs/PTs) that resulted in discontinuation are presented.

Table 13: Common AEsa – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**sotatercept + background therapy** **N = 20**	**placebo + background therapy** **N = 24**
ZENITH		
Overall rate of AEs[c]	19 (95.0)	23 (95.8)
Blood and lymphatic system disorders	7 (35.0)	4 (16.7)
Anaemia	2 (10.0)	1 (4.2)
Iron deficiency anaemia	2 (10.0)	1 (4.2)
Polycythaemia	2 (10.0)	0 (0)
Thrombocytopenia	3 (15.0)	2 (8.3)
Cardiac disorders	8 (40.0)	14 (58.3)
Cardiac failure	0 (0)	3 (12.5)
Palpitations	4 (20.0)	1 (4.2)
Right ventricular failure	2 (10.0)	5 (20.8)
Tachycardia	2 (10.0)	1 (4.2)
Ear and labyrinth disorders	4 (20.0)	2 (8.3)
Eye disorders	6 (30.0)	1 (4.2)
Vision blurred	2 (10.0)	1 (4.2)

Table 13: Common AEsa – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**sotatercept + background therapy** **N = 20**	**placebo + background therapy** **N = 24**
Gastrointestinal disorders	14 (70.0)	13 (54.2)
Abdominal pain	2 (10.0)	0 (0)
Abdominal pain upper	2 (10.0)	2 (8.3)
Diarrhoea	7 (35.0)	3 (12.5)
Gastrooesophageal reflux disease	2 (10.0)	0 (0)
Haematemesis	2 (10.0)	0 (0)
Haematochezia	2 (10.0)	0 (0)
Nausea	5 (25.0)	4 (16.7)
Vomiting	5 (25.0)	1 (4.2)
General disorders and administration site conditions	12 (60.0)	15 (62.5)
Chest discomfort	2 (10.0)	2 (8.3)
Fatigue	5 (25.0)	6 (25.0)
Peripheral oedema	2 (10.0)	6 (25.0)
Infections and infestations	16 (80.0)	15 (62.5)
COVID-19	4 (20.0)	3 (12.5)
Nasopharyngitis	4 (20.0)	3 (12.5)
Pneumonia	1 (5.0)	4 (16.7)
Sinusitis	3 (15.0)	0 (0)
Urinary tract infection	3 (15.0)	0 (0)
Injury, poisoning and procedural complications	5 (25.0)	2 (8.3)
Contusion	3 (15.0)	0 (0)
Fall	2 (10.0)	0 (0)
Examinations	7 (35.0)	6 (25.0)
Haemoglobin increased	2 (10.0)	1 (4.2)
Metabolism and nutrition disorders	12 (60.0)	11 (45.8)
Hypervolaemia	2 (10.0)	0 (0)
Hypokalaemia	5 (25.0)	5 (20.8)
Hypomagnesaemia	2 (10.0)	0 (0)
Iron deficiency	4 (20.0)	3 (12.5)

Table 13: Common AEsa – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	sotatercept + background therapy N = 20	placebo + background therapy N = 24
Musculoskeletal and connective tissue disorders	10 (50.0)	9 (37.5)
Arthralgia	4 (20.0)	3 (12.5)
Back pain	3 (15.0)	1 (4.2)
Muscle spasms	1 (5.0)	4 (16.7)
Musculoskeletal chest pain	2 (10.0)	0 (0)
Myalgia	2 (10.0)	1 (4.2)
Pain in jaw	2 (10.0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (15.0)	0 (0)
Nervous system disorders	11 (55.0)	11 (45.8)
Dizziness	2 (10.0)	3 (12.5)
Headache	7 (35.0)	8 (33.3)
Syncope	3 (15.0)	1 (4.2)
Psychiatric disorders	5 (25.0)	1 (4.2)
Renal and urinary disorders	3 (15.0)	6 (25.0)
Chronic kidney disease	2 (10.0)	0 (0)
Reproductive system and breast disorders	1 (5.0)	3 (12.5)
Respiratory, thoracic and mediastinal disorders	11 (55.0)	17 (70.8)
Cough	2 (10.0)	2 (8.3)
Dyspnoea	4 (20.0)	9 (37.5)
Nose bleed	7 (35.0)	1 (4.2)
Pulmonary arterial hypertension	0 (0)	10 (41.7)
Skin and subcutaneous tissue disorders	11 (55.0)	6 (25.0)
Eczema	2 (10.0)	0 (0)
Erythema	3 (15.0)	0 (0)
itching	2 (10.0)	0 (0)
Rash	2 (10.0)	1 (4.2)
Telangiectasia	5 (25.0)	1 (4.2)
Vascular disorders	5 (25.0)	5 (20.8)
Hypotension	4 (20.0)	3 (12.5)

a. Events that occurred in ≥ 10% of patients in at least one study arm.
b. MedDRA version 27.0; SOC and PT notation taken from Module 4 without adaptation.
c. Overall rate including disease-related events.

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 14: Common SAEsa – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	sotatercept + background therapy N = 20	placebo + background therapy N = 24
ZENITH		
Overall rate of SAEs[c]	12 (60.0)	17 (70.8)
Cardiac disorders	4 (20.0)	9 (37.5)
Atrial tachycardia	1 (5.0)	0 (0)
Cardiac failure	0 (0)	2 (8.3)
Right ventricular failure	2 (10.0)	5 (20.8)
Tachycardia	1 (5.0)	0 (0)
Gastrointestinal disorders	1 (5.0)	2 (8.3)
Haematemesis	1 (5.0)	0 (0)
Infections and infestations	4 (20.0)	6 (25.0)
Viral bronchitis	1 (5.0)	0 (0)
COVID-19	2 (10.0)	0 (0)
Influenza	1 (5.0)	0 (0)
Klebsiella bacteraemia	1 (5.0)	0 (0)
Pneumonia	0 (0)	4 (16.7)
Metabolism and nutrition disorders	4 (20.0)	2 (8.3)
Electrolyte imbalance	1 (5.0)	0 (0)
Hypervolaemia	1 (5.0)	0 (0)
Hypokalaemia	1 (5.0)	1 (4.2)
Hypomagnesaemia	1 (5.0)	0 (0)
Musculoskeletal and connective tissue disorders	1 (5.0)	0 (0)
Osteonecrosis of the jaw	1 (5.0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (10.0)	0 (0)
Adenocarcinoma gastric	1 (5.0)	0 (0)
Malignant melanoma	1 (5.0)	0 (0)
Metastatic malignant melanoma	1 (5.0)	0 (0)
Malignant neoplasm	1 (5.0)	0 (0)
Product-related problems	1 (5.0)	1 (4.2)
Dislocation of a medical device	1 (5.0)	0 (0)
Renal and urinary disorders	1 (5.0)	1 (4.2)
Chronic kidney disease	1 (5.0)	0 (0)

Table 14: Common SAEsa – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	**sotatercept + background therapy N = 20**	**placebo + background therapy N = 24**
Respiratory, thoracic and mediastinal disorders	0 (0)	12 (50.0)
Dyspnoea	0 (0)	2 (8.3)
Pulmonary arterial hypertension	0 (0)	9 (37.5)
Pulmonary arterial hypertension	0 (0)	2 (8.3)
Respiratory failure	0 (0)	2 (8.3)
Skin and subcutaneous tissue disorders	1 (5.0)	0 (0)
Skin ulceration	1 (5.0)	0 (0)
Surgical and medical procedures	1 (5.0)	0 (0)
Change in treatment	1 (5.0)	0 (0)
Vascular disorders	0 (0)	2 (8.3)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. MedDRA version 27.0; SOC and PT notation taken from Module 4 without adaptation.
c. Overall rate including disease-related events.

COVID-19: coronavirus disease 2019; 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 15: Discontinuation due to AEs – RCT, direct comparison: sotatercept + background therapy vs. placebo + background therapy

Study	Patients with event n (%)	
SOCa PTa	**sotatercept + background therapy N = 20**	**placebo + background therapy N = 24**
ZENITH		
Overall rate of discontinuations due to AEs[b]	0 (0)	1 (4.2)
Examinations	0 (0)	1 (4.2)
Electrocardiogram QT prolonged	0 (0)	1 (4.2)

a. MedDRA version 27.0; SOC and PT notation taken unmodified from Module 4.
b. Overall rate including disease-related events.

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