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Angiotensin II acetate (refractory hypotension in distributive shock) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Angiotensin-II-Acetat (refraktäre Hypotonie bei distributivem Schock) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 October 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Table of contents

List of tables[2]

Page

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

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
EMA	European Medicines Agency
ICU	intensive care unit
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAP	mean arterial pressure
mITT	modified intention to treat
NED	noradrenaline equivalence dose
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	standardized MedDRA query
SOFA	Sequential Organ Failure Assessment
SPC	Summary of Product Characteristics
SSC	Surviving Sepsis Campaign

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the active substance angiotensin II acetate. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 July 2021.

Research question

The aim of this report is to assess the added benefit of angiotensin II acetate in comparison with optimized standard therapy as the appropriate comparator therapy (ACT) in the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines or other available vasopressor therapies.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of angiotensin II acetate

Therapeutic indication	ACT[a]
Refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines or other available vasopressor therapies	Optimized standard therapy[b]
a. Presented is the ACT specified by the G-BA. b. Patients in both study arms are assumed to receive optimal intensive medical care. Standard therapy particularly includes fluid resuscitation, vasopressors, and antibiotics. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company follows the specification of the ACT but interprets it as optimized standard therapy which must consist of at least 2 vasopressors. This approach is not appropriate. According to the German S3 Guideline "Sepsis – prevention, diagnosis, therapy and follow-up care" and the Surviving Sepsis Campaign (SSC) guideline, patients who fail to respond to noradrenalin therapy can be treated with a second vasopressor. In acute and life-threatening emergencies, however, the investigator can also use other treatment strategies or therapies targeted to the individual patient. In addition, the guidelines do not provide any recommendations as to the noradrenaline dose starting at which a 2nd vasopressor is to be added. In disagreement with the company, the number of vasopressors used in the present situation was therefore not defined as a criterion for the implementation of optimized standard therapy.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 28 weeks were used for deriving the added benefit. A longer follow-up duration would be desirable, particularly for long-term survival and health-related quality of life.

Study pool and study design

The study pool for the present benefit assessment consists of the ATHOS-3 study.

The ATHOS-3 study is a randomized, double-blind study comparing angiotensin II acetate with placebo, each as an addition to vasopressor therapy. The study included adult patients with catecholamine-resistant hypotension, defined as those requiring a total sum catecholamine dose > 0.2 µg/kg/min for 6–48 hours to maintain a mean arterial pressure (MAP) of 55–70 mmHg and clinical features of high-output shock. Patients were to have received adequate volume resuscitation and have a cardiovascular Sequential Organ Failure Assessment (SOFA) score of 4.

A total of 344 patients were randomly allocated in a 1:1 ratio to treatment with either angiotensin II acetate (N = 172) or placebo (N = 172).

In the study, patients received vasopressor therapy 6 to 48 hours before randomization; this vasopressor therapy was optimized to achieve a target MAP ≥ 65 mmHg, where possible. Patients who met the inclusion criteria after this time period were then randomized to the treatment arms of angiotensin II acetate or placebo. Depending on MAP and treatment phase, the study drug and vasopressor therapy were adjusted for 48 hours in both study arms, but where possible, no changes in the vasopressor dose were to be carried out for the period 0 to 3 hours. Angiotensin II acetate was used mostly in accordance with the Summary of Product Characteristics (SPC).

The primary outcome of the study was MAP response rate after 3 hours. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity and adverse events (AEs).

Implementation of the ACT

Patients in the ATHOS-3 study received appropriate fluid therapy as well as treatment of the underlying illness through systemic anti-infectives.

The vasopressor therapy optimized before study start was to not be changed for 3 hours from the start of treatment with the study drug. Exceptions were possible if the patient remained hypotensive despite adjustment of the study drug or became hypertensive. Increasing the vasopressor dose was also possible at any time at the investigator's discretion. Average MAP increased within the first 3 hours even in patients in the placebo arm, and during this period, vasopressor therapy was adjusted in 47 patients in the placebo arm. Overall, despite the limitations in the first 3 hours, the ATHOS-3 study is therefore assumed to have provided

sufficiently optimized vasopressor therapy. The limitations nevertheless contribute to limited certainty of results.

All in all, the therapy used in the ATHOS-3 study can be deemed a sufficiently optimized standard therapy.

Total population of ATHOS-3 study as the relevant population

In Module 4 A, the company used a subpopulation of the ATHOS-3 study for the benefit assessment. This subpopulation comprises patients previously treated with at least 2 vasopressors. In accordance with the therapeutic indication of angiotensin II acetate, however, all patients who remained hypotensive despite prior vasopressor therapy are relevant for the benefit assessment. These patients are represented by the total population of the ATHOS-3 study. Therefore, this benefit assessment is based on the total population of the ATHOS-3 study.

Limited transferability of the ATHOS-3 study

The ATHOS-3 study is an international study with only 10% of patients being from Europe. ATHOS-3 study results cannot be fully extended to the German healthcare system since, in the ATHOS-3 study, European patients substantially differed from other patients with regard to their prognosis and the therapy used. In the countries in which the study was conducted, the available treatment options are similar to those approved in Germany and listed as treatment options by the S3 Guideline; however, actual routine medical practice apparently differs markedly. As an additional aspect, it is unclear to what extent the treatment of European patients reflects the German healthcare context since, even within Europe, different therapies are approved and standards in intensive care can vary. The limited transferability to the German healthcare context reduces the certainty of results.

Risk of bias

The risk of bias at study level was rated as low. The risk of bias of the results of each of the included outcomes is rated as low.

Summary assessment of the certainty of results

Due to limited transferability to the German healthcare context, the certainty of results of the ATHOS-3 study is deemed limited. In addition, the limitations in implementation of the ACT contribute to the limited certainty of results. Hence, irrespective of the low outcome-specific risk of bias, at most hints, e.g. of added benefit, can be derived on the basis of the available information for all outcomes.

Results

All-cause mortality (Day 28)

For the outcome of all-cause mortality, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of angiotensin II acetate + optimized

standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

Morbidity

Discontinuation of mechanical ventilation

For the outcome of discontinuation of mechanical ventilation, no usable data are available from the ATHOS-3 study. This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

Intensive care unit (ICU) discharge

For the outcome of ICU discharge, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

Discontinuation of renal replacement therapy

For the outcome of discontinuation of renal replacement therapy, no usable data are available from the ATHOS-3 study. This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

Health-related quality of life

The ATHOS-3 study did not survey any outcomes from the health-related quality of life category. This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

For the outcome of SAEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Specific AEs

Embolic and thrombotic events (SAEs), peripheral ischaemia (SAEs)

For each of the outcomes of embolic and thrombotic events (SAEs) and peripheral ischaemia (SAEs), no statistically significant difference between treatment groups was found. Consequently, for each of them, there is no hint of greater or lesser harm of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Arrhythmia

For the outcome of arrhythmia, no usable data are available from the ATHOS-3 study. Consequently, there is no hint of greater or lesser harm of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

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

On the basis of the presented results, the probability and extent of added benefit of the drug angiotensin II acetate in comparison with the ACT have been assessed as follows:

The ATHOS-3 study shows neither effects to the advantage nor to the disadvantage of angiotensin II acetate + optimized standard therapy. In summary, for refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies, there is no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of added benefit of angiotensin II acetate.

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

Table 3: Angiotensin II acetate – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Refractory hypotension in adults with septic or other distributive shock[b] who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies	Optimized standard therapy[c]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. The majority of ATHOS-3 study participants were patients with septic shock. It remains unclear whether the observed effects can be extended to patients with other distributive shock. c. Patients in both study arms are assumed to receive optimal intensive medical care. Standard therapy particularly includes fluid resuscitation, vasopressors, and antibiotics. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

2.2 Research question

The aim of this report is to assess the added benefit of angiotensin II acetate in comparison with optimized standard therapy as the ACT in the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines or other available vasopressor therapies.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of angiotensin II acetate

Therapeutic indication	**ACT**[a]
Refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines or other available vasopressor therapies	Optimized standard therapy[b]
a. Presented is the ACT specified by the G-BA. b. Patients in both study arms are assumed to receive optimal intensive medical care. Standard therapy particularly includes fluid resuscitation, vasopressors, and antibiotics. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company follows the specification of the ACT but interprets it as optimized standard therapy which must consist of at least 2 vasopressors. This approach is not appropriate. According to the German S3 Guideline "Sepsis – prevention, diagnosis, therapy and follow-therapy" and the SSC guideline, patients who do not respond to noradrenalin therapy can be treated with a second vasopressor [3,4]. In acute and life-threatening emergencies, however, the investigator can also use other treatment strategies or therapies targeted to the individual patient. In addition, the guidelines do not provide any recommendations as to the noradrenaline dose starting at which a 2nd vasopressor is to be added. In disagreement with the company, the number of vasopressors used in the present situation was therefore not defined as a criterion for the implementation of optimized standard therapy.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 28 weeks were used for deriving the added benefit. A longer follow-up duration would be desirable, particularly for long-term survival and health-related quality of life. This deviates from the company's inclusion criteria, which did not specify a minimum study duration.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- Study list on angiotensin II acetate (status: 17 May 2021)

- Bibliographic literature search on angiotensin II acetate (last search on 19 May 2021)
- Search in trial registries / study results databases on angiotensin II acetate (last search on 12 May 2021)
- Search on the G-BA website on angiotensin II acetate (last search on 19 May 2021)

To check the completeness of the study pool:

- Search in trial registries for angiotensin II acetate (last search on 5 August 2021); for search strategies, see Appendix A of the full dossier assessment.

In addition to the ATHOS-3 study, the check identified the ATHOS pilot trial as a potentially relevant study [5,6]. The ATHOS pilot trial is a randomized, controlled study comparing angiotensin II acetate with placebo, each as an add-on to vasopressor therapy. The study included 20 adult patients with high-output shock who had received sufficient prior fluid therapy, but did not respond to it. Vasopressor therapy consisted of noradrenaline and vasopressin, adrenalin, and/or phenylephrine. Patients were treated with placebo or angiotensin II acetate at doses of 5 to 40 ng/kg/min for 6 hours. The primary outcome of the study was change in noradrenaline dose. As a secondary outcome, 30-day mortality was surveyed.

Due to the limited information in the available sources, the relevance of the ATHOS pilot trial for the present benefit assessment cannot be definitively assessed. In particular, it is unclear whether patients had had catecholamine-resistant hypotension before being treated with angiotensin II acetate. It is also unclear which vasopressor therapy regimen was used and whether optimized standard therapy was implemented in the study. However, due to the very small study size (20 included patients; < 10% compared to the ATHOS-3 study; N = 321), the results of this study presumably do not materially influence the result of the benefit assessment.

Because of its short treatment duration of 6 hours, the company excluded the ATHOS pilot trial from the benefit assessment. However, no minimum treatment duration has been defined for angiotensin II acetate in the current therapeutic indication [7]. Instead, treatment is to be discontinued after sufficient improvement of the underlying shock. Therefore, the completeness of the study pool was checked without regard to the treatment duration of angiotensin II acetate. Since no study other than the described ATHOS pilot trial was found, the company's approach is, overall, without consequence for the present benefit assessment.

2.3.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
LJ501-CRH01 (ATHOS-3[d])	Yes	Yes	No	Yes [8]	Yes [9,10]	Yes [11-20]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the tables below, the study will be referred to using this acronym.

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

The study pool for the benefit assessment of angiotensin II acetate versus the ACT consists of the ATHOS-3 study, as likewise defined by the company.

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
ATHOS-3	RCT, double-blind, parallel-group	Adults ≥ 18 years of age with catecholamine-refractory hypotension[b] with ▪ adequate volume resuscitation[c] ▪ Clinical high-output shock, characterized by: ▫ central venous oxygen saturation > 70% and CVP > 8 mmHg or ▫ cardiac index > 2.3 L/min/m^2 ▪ cardiovascular SOFA score = 4	Angiotensin II acetate (N = 172) Placebo (N = 172)	Screening: 6–48 hours Treatment: up to 48 hours; if necessary, reinitiation of treatment up to 168 hours[d] Follow-up observation: up to 28 days[e]	124–centres in: Australia, Belgium, Canada, Finland, France, Germany, New Zealand, United Kingdom, United States 05/2015–02/2017	Primary: response rate (MAP) after 3 hours[f] Secondary: all-cause mortality, morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Defined as total sum catecholamine dose > 0.2 µg/kg/min for 6 to 48 hours to maintain a MAP of 55–70 mmHg.
c. An inclusion criterion was for patients to have received at least 25 mL/kg of crystalloid or colloid solution over the previous 24-hour period and to exhibit adequate volume resuscitation in the investigator's opinion.
d. At a cardiovascular SOFA score of 4, treatment could be reinitiated within 3 hours after discontinuation.
e. A follow-up observation of 28 days was not ensured for all patient-relevant outcomes; see Section 2.4.1 for outcomes with a shorter follow-up duration.
f. Response was defined as MAP ≥ 75 mmHg or an increase by ≥ 10 mmHg from baseline without increase in the noradrenaline equivalence dose.

AE: adverse event; CVP: central venous pressure; MAP: mean arterial pressure; N: number of randomized patients; n: subpopulation analysed by the company; RCT: randomized controlled trial; SOFA: Sequential Organ Failure Assessment

Table 7: Characterization of the intervention – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study	Intervention	Comparison
ATHOS-3	Angiotensin II acetate i.v.: Treatment phases: ▪ 0–3 hours: initial dose 20 ng/kg/min, then 2.5[a]-200 ng/kg/min titrated using MAP target range 1 (≥ 75 mmHg to < 85 mmHg) ▪ 3–48 hours: 2.5[a]–40 ng/kg/min as per MAP target range 2 (65−70 mmHg) ▪ After 48 hours: incremental dose reduction by at most 10 ng/kg/min every 15 minutes until discontinuation ▪ Within 3 hours after discontinuation: if necessary[b], reinitiation of therapy (2.5[a]–40 ng/kg/min); incremental discontinuation after 7 days (168 hours) at the latest + vasopressor therapy (see below)	Placebo i.v. + vasopressor therapy (see below)
	▪ Dose adjustments for angiotensin II acetate or placebo based on tolerability and achievement of MAP target range (minimum dose: 1.25 ng/kg/min[a]); treatment discontinuation in case of toxicity on minimum dose ▪ Vasopressor therapy (by treatment phases): ▫ 6–48 hours before treatment start: optimization with a MAP target range of ≥ 65 mmHg[c] ▫ 0–3 hours: - stable vasopressor dose; uptitration allowed in case of immediate need - At MAP ≥ 85mmHg and minimum dose of study drug: discontinuation of vasopressin (if used); if MAP remains ≥ 85 mmHg: weaning of catecholamines ▫ 3–48 hours: - at MAP ≥ 70 mmHg: discontinuation of vasopressin (if used); if MAP remains ≥ 70 mmHg: weaning of catecholamines	
	Nonpermitted prior treatment ▪ Standing dose > 500 mg/day of hydrocortisone or equivalent **Necessary prior treatment** ▪ At least 25 mL/kg of a crystalloid or colloid solution over the 24-hour period before treatment start ▪ Vasopressor therapy (see above) **Permitted concomitant treatment** ▪ Continuation of supportive therapies from before study start ▪ Treatment of concomitant diseases (e.g. systemic anti-infectives) ▪ ≤ 750 mL i.v. fluids in the first 3 hours of treatment ▪ Inotropic agents such as dobutamine or milrinone (except adrenaline and dopamine in inotropically effective doses)	

a. In hyper-responders (MAP ≥ 85mmHg in the period 0–3 hours, or ≥ 70mmHg from hour 3 despite discontinuation of vasopressin and discontinuation or dose reduction of catecholamines), the dose of the study drug should be reduced to 1.25 ng/kg/min.
b. Cardiovascular SOFA score = 4.
c. According to Module 4, the target range was 55–70 mmHg, with a reading ≥ 65 mmHg being preferable.

i.v.: intravenous; MAP: mean arterial pressure; RCT: randomized controlled trial; SOFA: Sequential Organ Failure Assessment;

Study design

The ATHOS-3 study is a randomized, double-blind study comparing angiotensin II acetate with placebo, each as an addition to vasopressor therapy. The multicentric study was conducted in North America, Australia, and Europe. The study included adult patients with catecholamine-refractory hypotension, defined as a total sum catecholamine dose > 0.2 µg/kg/min for 6–18 hours to maintain a MAP of 55–70 mmHg and clinical high-output shock (see Table 6 for a definition). Patients were to have received adequate volume resuscitation and have a cardiovascular SOFA score of 4.

A total of 344 patients were randomly allocated in a 1:1 ratio to treatment with either angiotensin II acetate (N = 172) or placebo (N = 172). Randomization was stratified by MAP at screening visit (< 65 / ≥ 65 mmHg) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (≤ 30 / 31−40 / ≥ 41points). Of those randomized, 163 patients in the angiotensin II arm and 158 in the placebo arm were treated with the study medication (modified intention to treat population, mITT). All information stated below is based on the mITT population.

At 6–48 hours before randomization, study participants received vasopressor therapy which was optimized to reach a target MAP of ≥ 65 mmHg, if possible. Patients who met the inclusion criteria after this time period were then randomized to the treatment arms of angiotensin II acetate or placebo. Depending on treatment phase and MAP, the study drug and vasopressor therapy were adjusted for 48 hours in both study arms, although for the period 0–3 hours, changes in the vasopressor dose were to be avoided, if possible (see section below for a discussion on the implementation of the ACT). While in the angiotensin II arm, a maximum dose of 200 ng/kg/min was allowed in the period 0–3 hours, the approved maximum dose of angiotensin II acetate is 80 ng/kg/min [7]. In this period, about 16% of patients received a dose above the approved maximum dose. Other than that, angiotensin II acetate was used in accordance with the SPC.

Patients were treated for an average of 47 hours in the angiotensin II arm and 40 hours in the placebo arm. All patients were to be followed up for at least 7 days (or at least 3 days after discontinuation of the study drug). Further, an additional follow-up 28 days after treatment start was planned.

The primary outcome of the study was MAP response rate after 3 hours. Patient-relevant secondary outcomes were all-cause mortality as well as outcomes on morbidity and AEs.

Implementation of the ACT

The G-BA defined the ACT to be optimized standard therapy, which particularly includes fluid administration, vasopressor therapy, and antibiotic therapy.

A prerequisite for inclusion in the ATHOS-3 study was for patients to have received fluid therapy with at least 25 mL/kg of a crystalloid or colloid solution before the start of vasopressor

therapy and that, according to the investigator, they had received adequate volume resuscitation. Following initial fluid therapy, further administration of fluids should ideally be avoided, but administering up to 750 mL fluid within the first 3 hours of treatment was allowed. The fluid therapy used in the ATHOS-3 study is generally in line with the recommendations of the German S3 Guideline and the SSC guideline [3,4]. While the guidelines recommend the use of crystalloids, this recommendation is based merely on the fact that colloids are associated with higher costs. The use of colloids (in addition to crystalloids) in the ATHOS-3 study is therefore appropriate. While the guidelines recommend a volume of at least 30 mL/kg for initial fluid resuscitation, patients' baseline central venous pressure (CVP) was about 13 mmHg and hence slightly above the target of 8−12mmHg, which is recommended for "early goal-directed therapy" [21]. Overall, the fluid therapy used in the ATHOS-3 study was therefore deemed adequate.

Following fluid therapy, patients received vasopressor therapy, which was adjusted 6−48 hours before starting the study drug, aiming for a target MAP of ≥ 65 mmHg, if possible. All patients except one received noradrenaline. About 51% of patients additionally received another vasopressor, and about 20% had more than 2 vasopressors. At treatment start, patients had achieved an average MAP of 66 mmHg. From the start of treatment with the study drug, no further changes were to be made to the vasopressor dose for 3 hours. Exceptions were possible if the patient remained hypotensive (MAP ≤ 59 mmHg) or became hypertensive (MAP ≥ 85 mmHg) despite adjustment of the study drug (see Table 7). In addition, it was possible to increase the vasopressor dose at any time upon the investigator's discretion.

The average MAP over the course of treatment increased within the first 3 hours even in the placebo arm (see Figure 1). In addition, the company reports that, within the first 3 hours, 47 patients in the placebo arm received adjustments in vasopressor therapy. Overall, despite the limitations in the first 3 hours, the ATHOS-3 study is therefore assumed to have provided sufficiently optimized vasopressor therapy. However, the limitations contribute to limited certainty of results (see Section 2.4.2).

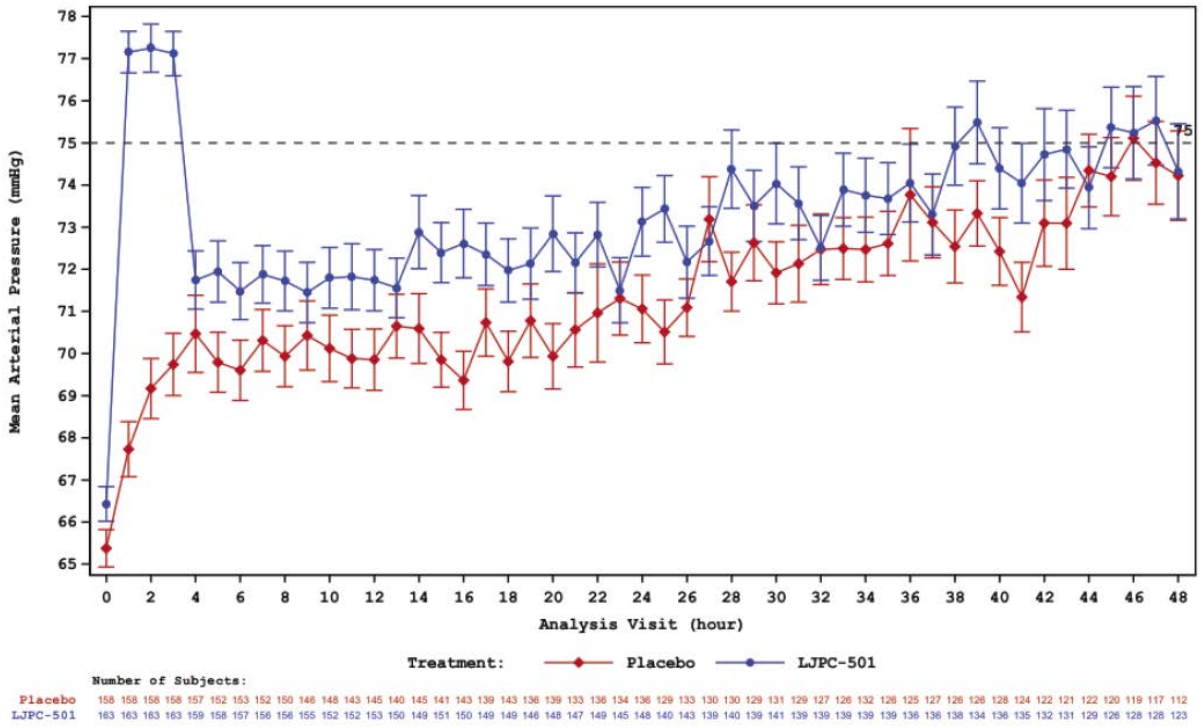

Figure 1: Average MAP during the first 48 hours of treatment in the ATHOS-3 study.

Further, standard therapy also includes antibiotic treatment. In the ATHOS-3 study, about 99% of patients were treated with systemic anti-infectives. No additional information, e.g. on treatment type and dose, is available, but the company reported that all patients with suspected or confirmed sepsis certainly received antibiotics. In addition, the company maintains that, in the present life-threatening situation, all antibiotic treatment options can be assumed to have been exhausted and that, as per routine practice, treatment was adjusted after the pathogen was identified. For the benefit assessment, patients in the study were assumed to have received adequate antibiotic therapy for the underlying illness (about 80% of patients had sepsis).

In summary, patients in the ATHOS-3 study received (a) adequate fluid therapy, (b) vasopressor therapy which could be adjusted according to the physician's discretion as well as (c) systemic anti-infectives for the underlying illness. While the protocol placed restrictions on some therapies, adequate patient care can be assumed in the present situation. All in all, the therapy used in the ATHOS-3 study can therefore be deemed sufficiently optimized standard therapy. However, the certainty of results is reduced by limited transferability to the German healthcare context (see section on the transferability of the study results to the German healthcare context below).

Total population of ATHOS-3 study as the relevant population

In Module 4 A, the company used a subpopulation of the ATHOS-3 study for the benefit assessment. This subpopulation comprises patients who had been previously treated with at least 2 vasopressors (229 of 321 patients; 71.3%). The company justifies this approach by

arguing that in this subpopulation, the ACT defined by the G-BA was adequately implemented by the prior use of at least 2 vasopressors. As described in Section 2.2, the ACT consists of optimized standard therapy, which particularly includes fluid therapy, vasopressors, and antibiotics. No minimum number of vasopressors is defined. Additionally, in acute and life-threatening situations, different treatment strategies are possible upon the physician's discretion. In line with the therapeutic indication of angiotensin II acetate, all patients who remained hypotensive despite prior vasopressor therapy are therefore relevant for the benefit assessment. These patients are represented by the total population of the ATHOS-3 study. The subpopulation used by the company, in contrast, represents only a subgroup of the relevant population. In disagreement with the company, this benefit assessment therefore uses the total population of the ATHOS-3 study.

Characterization of the study population

Table 8 shows the patient characteristics of the included study.

Table 8: Characterization of the study population – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Characteristic Category	**Angiotensin II acetate + optimized standard therapy N[a] = 163**	**Placebo + optimized standard therapy N[a] = 158**
ATHOS-3		
Age [years], mean (SD)	62 (16)	63 (15)
Sex [f/m], %	44/56	35/65
Region, n (%)		
USA/Canada	116 (71)	120 (76)
Europe	19 (12)	14 (9)
Australia / New Zealand	28 (17)	24 (15)
MAP [mmHg], mean (SD)		
At screening visit	65.5 (3.5)	65.4 (3.8)
At treatment start	66.4 (5.3)	65.4 (5.6)
$ScvO_2$ [%], mean (SD)	77.6 (8.9)[b]	77.2 (8.6)[b]
CVP [mmHg], mean (SD)	13.7 (5.1)[c]	12.8 (4.7)[c]
Cardiac index [L/min/m^2], mean (SD)	3.3 (0.9)[d]	3.4 (1.0)[d]
APACHE II score at treatment start [points], mean (SD)	27.3 (8.4)	28.7 (8.3)
SOFA score at screening visit [points], mean (SD)	11.8 (2.8)	12.7 (3.3)
MELD score at treatment start [points], mean (SD)	20.4 (7.5)	21.9 (7.3)
ARDS based on X-ray findings, n (%)	40 (25)	51 (32)
Cause of distributive shock, n (%)		
Sepsis	127 (78)	132 (84)
Suspected sepsis	20 (12)	11 (7)
Vasoplegia	10 (6)	9 (6)
Pancreatitis	6 (4)	4 (3)
Other	0 (0)	2 (1)
Number of vasopressors at treatment start, mean (SD)	1.9 (0.8)	2.0 (0.7)
Number of vasopressors at treatment start, n (%)		
1	49 (30)	43 (27)
2	81 (50)	83 (53)
3	26 (16)	28 (18)
4	7 (4)	4 (3)
Vasopressin use[e], n (%)	113 (69)	111 (70)
NED at treatment start [µg/kg/min], mean (SD)	0.45 (0.35)	0.48 (0.45)
Treatment discontinuation up to Hour 48[f,g], n (%)	60 (37)	57 (36)
Treatment discontinuation before Day 28[h,i], n (%)	75 (46)[j]	86 (54)[j]

Table 8: Characterization of the study population – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Characteristic Category	Angiotensin II acetate + optimized standard therapy N[a] = 163	Placebo + optimized standard therapy N[a] = 158

a. Number of randomized patients who received the study drug (mITT). Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. Values are available for only 120 patients (74%) in the angiotensin II arm and 117 patients (74%) in the placebo arm.
c. Values are available for only 126 patients (77%) in the angiotensin II arm and 123 patients (78%) in the placebo arm.
d. Values are available for only 69 patients (42%) in the angiotensin II arm and 73 patients (46%) in the placebo arm.
e. During the 6 hours prior to randomization.
f. No information is available on the number of patients who discontinued therapy after more than 48 hours.
g. Main reasons for treatment discontinuation were patient death (21 versus 29 patients) as well as MAP improvement (32 versus 16 patients).
h. Discrepant data found in Module 4 versus the study report; the presented figures are from the study report.
i. The most common reason for study discontinuation was patient death (75 versus 85 patients).
j. IQWiG calculations:

APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: acute respiratory distress syndrome; CVP: central venous pressure; f: female; IQWiG: Institute for Quality and Efficiency in Health Care; m: male; MAP: mean arterial pressure; MELD: Model of Endstage Liver Disease; mITT: modified intention to treat; n: number of patients in the category; N: number of randomized and treated patients; NED: noradrenaline equivalence dose; RCT: randomized controlled trial; $ScvO_2$: central venous oxygen saturation; SD: standard deviation; SOFA: Sequential Organ Failure Assessment

Both study arms were very similar in terms of patients' demographic and clinical characteristics. Most patients were from the United States or Canada, and their average age was 63 years. At 60%, the percentage of men was slightly higher than that of women.

In the majority of patients, the cause of distributive shock was sepsis or suspected sepsis. Patients had an average SOFA score of about 12 and an APACHE II score of 28. Some 70% of patients received prior therapy with at least 2 vasopressors. Vasopressin was used in about 70% of patients.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study	Adequate random sequence generation	Allocation concealment	Blinding		Results-independent reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
ATHOS-3	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the ATHOS-3 study. This concurs with the company's assessment.

Transferability of the study results to the German healthcare context

The ATHOS-3 study is an international study; of the included patients, most were from North America, and only about 10% from Europe. The company's dossier therefore discusses at length the transferability of study results to the German healthcare context and describes, in particular, the study population and the therapies used in the study (vasopressors, fluid therapy, and anti-infectives).

In the description of the study population, the company compares the characteristics of patients from the various geographic regions, concluding that there seem to be differences in the patient populations. For instance, the company reports a better average prognosis (as measured by the APACHE II score and SOFA score) at baseline in European patients. Further, the company discusses regional differences in hospital care, such as the number of ICU beds, length of ICU stay, or time of admittance to the ICU.

With regard to the therapies used in the study, the company also describes differences between geographic regions. On average, European patients received a much higher noradrenaline equivalence dose (NED). Simultaneously, it was less common for a second vasopressor to be added to therapy. In this context, the company discusses the recommendations of the German S3 Guideline and the SSC guideline. The company reports that the recommendations regarding the type of first-line therapy are harmonized worldwide, but that there are no concrete recommendations with regard to the duration and dose of therapy or the time a second vasopressor is added. Regarding fluid therapy, the company reports that, in Europe, crystalloid solutions are primarily used. The precise use of crystalloid versus colloid solutions in the ATHOS-3 study is unknown, but the company nevertheless assumes transferability to the German healthcare context since all patients received sufficient fluids and the type of fluid therapy likely was of little influence. Regarding systemic anti-infectives, the company suspects

that the resistance situation differs not only among countries but also among individual centres and expects the same to be the case within Germany.

Despite regional differences in patient characteristics, patient care, and vasopressor therapy, the company assumes the study results to be transferable to the German healthcare context overall. The company substantiates this conclusion mainly by differences in care even within Germany, by vasoactive therapy being individualized upon the physician's discretion, and by the ATHOS-3 study reflecting these differences. The company adds that the mortality of septic shock patients in Germany does not materially differ from mortality in the ATHOS-3 study.

Limited transferability of the ATHOS-3 study

Contrary to the company's assessment, the results of the ATHOS-3 study are not fully transferable to the German healthcare context. European participants of the ATHOS-3 study differ markedly from the other patients with regard to their prognosis and the therapy used. In the countries in which the study was conducted, the available treatment options are similar to those approved in Germany and listed as treatment options by the S3 Guideline; however, actual routine medical practice apparently differs markedly. These differences have been discussed by the European Medicines Agency (EMA) as early as during the approval process. In particular, the low percentage of ATHOS-3 participants with high NED was deemed to poorly represent European realities of care [20]. As a condition for granting the marketing authorization, the EMA required a phase IV study in which, e.g. at least 50% of patients were to be recruited in Europe. Moreover, it is unclear to what extent the treatment of European patients reflects the German healthcare context since, even within Europe, different therapies are approved and standards in intensive care can vary.

In summary, the results of the ATHOS-3 study are therefore transferable to the German healthcare context only to a limited extent. This reduces the certainty of results; therefore, regardless of bias aspects, at most hints, e.g. of added benefit, can be derived for all outcomes.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - Discontinuation of mechanical ventilation
  - ICU discharge
  - Discontinuation of renal replacement therapy
- Health-related quality of life

- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Embolic and thrombotic events (standardized MedDRA query [SMQ], SAEs)
  - Peripheral ischaemia (preferred term [PT], SAEs)
  - Arrhythmia
  - Further 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 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study	Outcomes										
	All-cause mortality	**Discontinuation of mechanical ventilation**	**ICU discharge**	**Discontinuation of renal replacement therapy**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**	**Embolic and thrombotic events (SMQ, SAEs)**	**Peripheral ischaemia (PT, SAEs)**	**Arrhythmia**	**Further specific AEs**
ATHOS-3	Yes	No[a]	Yes	No[a]	No[b]	Yes[c]	Yes[c]	Yes[c]	Yes[c]	No[a]	No[d]

a. No usable data available; for reasoning, see body of text below.
b. Outcome not recorded.
c. Side effects of the intervention cannot be distinguished from symptoms of the underlying illness; for an explanation, see body of text below.
d. No further specific AEs were identified.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA query

Note on outcomes of the morbidity category

- Discontinuation of mechanical ventilation: This outcome is defined as the period between treatment start and end of mechanical ventilation. For this outcome, the company presents analyses with a follow-up period of 7 days. However, the results presented by the company show that, after 7 days, the majority of patients was still on mechanical

ventilation; thus the median was not reached in this analysis. The follow-up duration of 7 days is therefore too short for obtaining results of informative value. Hence, no usable data are available for this outcome.

- Discontinuation of renal replacement therapy: This outcome is defined as the period between treatment start and discontinuation of renal replacement therapy and was analysed post hoc as a condition for the granting of a marketing authorization. For this outcome, the company presented analyses which included only patients who, at treatment start, had suffered acute renal failure requiring renal replacement therapy. However, in the present therapeutic indication, all patients are generally at risk of developing acute renal failure during the study period due to the potential deterioration of organ function. At the start of the ATHOS-3 study, 45 patients (27.6%) in the angiotensin II arm and 60 patients (38.0%) in the placebo arm received renal replacement therapy. Given these small percentages of patients undergoing renal replacement therapy at study start, it is not permissible to draw any conclusions concerning all study participants. Further, the company has presented analyses with only a follow-up period of 7 days for this outcome. The results submitted by the company show, however, that after 7 days, the majority of patients still required renal replacement therapy, meaning that the median was not reached in this analysis. The follow-up duration of 7 days is therefore too short for obtaining results of informative value. Overall, no usable data are therefore available for this outcome.

Note on outcomes of the side effects category

- SAEs, discontinuation due to AEs, and specific AEs: In the ATHOS-3 study, AEs were followed up for 7 days, while SAEs and AEs of special interest were followed up until Day 28. In the present therapeutic indication, the AEs which occurred exhibited strong overlap with events due to the underlying illness. For the subpopulation it used in the assessment, the company submitted analyses excluding events of the Standardized MedDRA Query (SMQ) of toxic-septic shock conditions. But even this type of analysis precludes an isolated consideration of AEs because the underlying illness manifests in a myriad of different symptoms caused by multiple organ failures, which makes it impossible to clearly distinguish side effects of the intervention from events of the underlying illness. Below, results on side effects, which include AEs due to symptoms of the underlying illness, are interpreted as a mixture of symptoms and side effects.
- Arrhythmia: For arrhythmia, the study protocol specified an analysis of the SMQ arrhythmia and the SMQ torsade de pointes/QT prolongation. Instead of this predefined analysis, the company's Module 4 A presents analyses grouped under "cardiac AEs of special interest". The company does not discuss the events included in this analysis. However, results reveal that the analysis includes acute myocardial infarctions which are not deemed arrythmias as per the predefined analysis through SMQs. The company did not present the results of the predefined analysis. For the outcome of arrhythmias, no usable data are therefore available.

Primary outcome of MAP response rate not included

MAP describes the average blood pressure during one cardiac cycle [22]. In medicine, MAP is used as an indicator of organ perfusion. The German S3 guideline and the SSC guideline define a MAP target of at least 65 mmHg for the treatment of hypotension in patients with septic shock [3,4]. In the ATHOS-3 study, MAP response rate was investigated as a primary outcome. The company's dossier submits the following MAP analyses:

- MAP response rate: Analyses of the percentages of patients who achieved a MAP ≥ 75 mmHg or MAP improvement by ≥ 10 mmHg by Hour 3; need for a vasopressor dose increase during this time period resulted in rating as treatment failure.
- Analysis of change in MAP between treatment start and Hour 3 or Hour 48

While the company's dossier states that MAP has not been validated as a surrogate for mortality, the company used MAP as a directly patient-relevant outcome in the morbidity category. The company did not state whether or to what extent MAP represents a valid surrogate for a patient-relevant outcome of the morbidity category. In departure from the company, the outcome of MAP is disregarded in the benefit assessment since a change in MAP is not directly patient relevant. This acute disease situation requires a direct survey of improvements in health status and symptoms, and such surveys are feasible.

2.4.2 Risk of bias

Table 11 presents the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias at study and outcome levels – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study		Outcomes										
	Study level	All-cause mortality	Discontinuation of mechanical ventilation	ICU discharge	Discontinuation of renal replacement therapy	Health-related quality of life	SAEs	Discontinuation due to AEs	Embolic and thrombotic events (SMQ, SAEs)	Peripheral ischaemia (PT, SAEs)	Arrhythmia	Further specific AEs
ATHOS-3	L	L	–[a]	L	–[a]	–[b]	L	L	L	L	–[a]	–

a. No usable data available; see Section 2.4.1 for the reasoning.
b. Outcome not recorded.

AE: adverse event; L: low; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA query

Concurring with the company, the risk of bias for each of the included outcomes is rated as low. For the outcome of discontinuation of mechanical ventilation, discontinuation of renal replacement therapy, and arrhythmia, no usable data are available; therefore, the risk of bias was not assessed.

Summary assessment of the certainty of results

Due to limited transferability to the German healthcare context (see Section 2.3.2), the certainty of results of the ATHOS-3 study is deemed limited. In addition, the limitations in implementation of the ACT contribute to the limited certainty of results. Hence, irrespective of the low outcome-specific risk of bias, at most hints, e.g. of added benefit, can be derived on the basis of the available information for all outcomes.

2.4.3 Results

Table 12 and Table 13 summarize the results of the comparison of angiotensin II acetate + optimized standard therapy versus placebo + optimized standard therapy for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines or other available vasopressor therapies. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

The results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix B of the full dossier assessment. The Kaplan-Meier curves of the outcomes of all-cause mortality and ICU discharge are presented in Appendix C of the full dossier assessment.

Table 12: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study **Outcome category** **Outcome**	**Angiotensin II acetate + optimized standard therapy**		**Placebo + optimized standard therapy**		**Angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy**
	N	**Median time to event in days [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in days [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
ATHOS-3					
Mortality					
All-cause mortality (Day 28)	163	NR [19.12; NR] 75 (46.0)	158	15.50 [10.03; NR] 85 (53.8)	0.78 [0.57; 1.07]; 0.123
Morbidity					
Discontinuation of mechanical ventilation	No usable data[b]				
ICU discharge	163	16 [14; 20] 72 (44.2)	158	17 [14; 20] 62 (39.2)	0.99 [0.71; 1.39]; 0.957
Discontinuation of renal replacement therapy	No usable data[b]				
Health-related quality of life	Outcome not surveyed				

a. Cox proportional hazards model and log rank test.
b. See Section 2.4.1 for the rationale.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; RCT: randomized controlled trial

Table 13: Results (side effects) – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study Outcome category Outcome	Angiotensin II acetate + optimized standard therapy		Placebo + optimized standard therapy		Angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ATHOS-3					
Side effects[b]					
AEs (supplementary information)	163	142 (87.1)	158	145 (91.8)	–
SAEs	163	99 (60.7)	158	106 (67.1)	0.91 [0.77; 1.07]; 0.258
Discontinuation due to AEs	163	23 (14.1)	158	34 (21.5)	0.66 [0.41; 1.06]; 0.085
Embolic and thrombotic events (SMQ, SAEs)	163	9 (5.5)	158	4 (2.5)	2.18 [0.69; 6.94]; 0.226
Peripheral ischaemia (PT, SAEs)	163	5 (3.1)	158	3 (1.9)	1.62 [0.39; 6.65]; 0.539
Arrhythmia	No usable data[c]				

a. IQWiG calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [23]).
b. Side effects of the intervention cannot be differentiated from symptoms of the underlying illness; see Section 2.4.1 for more information.
c. See Section 2.4.1 for a rationale.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query

Due to the limited transferability to the German healthcare context (see Sections 2.3.2 and 2.4.2), at most hints, e.g. of added benefit, can be derived on the basis of the available information.

Mortality

All-cause mortality (Day 28)

For the outcome of all-cause mortality, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

This departs from the assessment by the company, which derived added benefit based on the subpopulation it defined, finding an indication of added benefit for the outcome of all-cause mortality on the basis of these analyses.

Morbidity

Discontinuation of mechanical ventilation

For the outcome of discontinuation of mechanical ventilation, no usable data are available from the ATHOS-3 study (see Section 2.4.1). This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

This departs from the company's assessment in that the company based its assessment on the subpopulation it defined. On the basis of these analyses, however, the company also arrived at the conclusion that there is no evidence of added benefit.

ICU discharge

Operationalization

The outcome of ICU discharge is defined as the period between treatment start and ICU discharge up to Day 28. In cases where ICU discharge coincided with the day of death, patients were to be censored at that time.

Results

For the outcome of ICU discharge, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

This departs from the company's assessment in that the company based its assessment on the subpopulation it defined. On the basis of these analyses, however, the company also arrived at the conclusion that there is no evidence of added benefit.

Discontinuation of renal replacement therapy

For the outcome of discontinuation of renal replacement therapy, no usable data are available from the ATHOS-3 study (see Section 2.4.1). This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

This departs from the company's assessment. The company based its assessment on the subpopulation it defined and derived from these analyses an indication of added benefit.

Health-related quality of life

The ATHOS-3 study did not survey any outcomes from the health-related quality of life category. This results in no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

This departs from the company's assessment in that the company assessed added benefit on the basis of the subpopulation it defined. However, on the basis of these analyses, the company likewise arrives at the conclusion that there is no evidence of greater or lesser harm regarding the outcome of SAEs.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

This departs from the company's assessment. The company based its assessment on the subpopulation it defined and derived from these analyses an indication of lesser harm for the outcome of discontinuation due to AEs.

Specific AEs

Regarding specific AEs from which to derive added benefit, the company used any AEs where it found a statistically significant difference between treatment groups in the subpopulation it used for assessment as well as events designated as AEs of special interest. For the specific AEs included in the benefit assessment, no uniform evaluation of added benefit by the company is therefore available. Consequently, a description of the extent to which each individual conclusion on added benefit departs from that submitted by the company has been deliberately omitted.

Embolic and thrombotic events (SAEs), peripheral ischaemia (SAEs)

For each of the outcomes of embolic and thrombotic events (SAEs) and peripheral ischaemia (SAEs), no statistically significant difference between treatment groups was found. Consequently, for each of them, there is no hint of greater or lesser harm of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Arrhythmia

For the outcome of arrhythmia, the ATHOS-3 study provides no usable data (see Section 2.4.1). Consequently, there is no hint of greater or lesser harm of angiotensin II acetate + optimized

standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- Sex (male/female)
- Age (< 65 / ≥ 65 years)
- APACHE II score (≤ 30 points / > 30 points)

The listed subgroup characteristics were all predefined. The company submitted a full set of corresponding subgroup analyses for the subpopulation it used for assessment. Subgroup analyses for the total population, in contrast, are available only for the outcome of all-cause mortality.

Interaction tests were performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results showing 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.

Using the above-described methods, the available subgroup analyses on the outcome of all-cause mortality do not reveal any effect modifications.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes have been taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

On the basis of the results presented in Section 2.4, the extent of the respective added benefit at outcome level was estimated (see Table 14).

Table 14: Extent of added benefit at outcome level: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Outcome category **Outcome**	**Angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy** **Median time to event (days) or event rate (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	Median: NR vs. 15.50 HR: 0.78 [0.57; 1.07] p = 0.123	Lesser/added benefit not proven
Morbidity		
Discontinuation of mechanical ventilation	No usable data	Lesser/added benefit not proven
ICU discharge	Median: 16 vs. 17 HR: 0.99 [0.71; 1.39] p = 0.957	Lesser/added benefit not proven
Discontinuation of renal replacement therapy	No usable data	Lesser/added benefit not proven
Health-related quality of life		
Outcome not surveyed		
Side effects[c]		
SAEs	60.7% vs. 67.1% RR: 0.91 [0.77; 1.07] p = 0.258	Greater/lesser harm not proven
Discontinuation due to AEs	14.1% vs. 21.5% RR: 0.66 [0.41; 1.06] p = 0.085	Greater/lesser harm not proven
Embolic and thrombotic events (SAEs)	5.5% vs. 2.5% RR: 2.18 [0.69; 6.94] p = 0.226	Greater/lesser harm not proven
Peripheral ischaemia (SAEs)	3.1% vs. 1.9% RR: 1.62 [0.39; 6.65] p = 0.539	Greater/lesser harm not proven
Arrhythmia	No usable data	Greater/lesser harm not proven

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. Side effects of the intervention cannot be distinguished from symptoms of the underlying illness; see Section 2.4.1 for a discussion.

AE: adverse event; CI: confidence interval; CI_u: upper confidence limit; HR: hazard ratio; NR: not reached; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 15: Favourable and unfavourable effects from the assessment of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy

Favourable effects	**Unfavourable effects**
–	–
Outcomes from the category of health-related quality of life were not surveyed.	

The ATHOS-3 study shows neither effects to the advantage nor to the disadvantage of angiotensin II acetate + optimized standard therapy. In summary, for refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies, there is no hint of added benefit of angiotensin II acetate + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven.

Table 16 presents a summary of the results of the benefit assessment of angiotensin II acetate in comparison with the ACT.

Table 16: Angiotensin II acetate – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Refractory hypotension in adults with septic or other distributive shock[b] who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies	Optimized standard therapy[c]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. The majority of ATHOS-3 study participants were patients with septic shock. It remains unclear whether the observed effects can be extended to patients with other distributive shock. c. Patients in both study arms are assumed to receive optimal intensive medical care. Standard therapy particularly includes fluid resuscitation, vasopressors, and antibiotics. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit from the subpopulation it used for the evaluation.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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