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Angiotensin II acetate (refractory hypotension in distributive shock) –

Addendum to Commission A21-95[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Erika Baumbach
- Moritz Felsch
- Florina Kerekes
- Katrin Nink
- Katharina Wölke

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
APACHE II	Acute Physiology and Chronic Health Evaluation II
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICU	intensive care unit
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment

1 Background

On 23 November 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-95 (Angiotensin II acetate– benefit assessment according to §35a Social Code Book V) [1].

The randomized controlled trial (RCT) ATHOS-3 was included for the benefit assessment of angiotensin II acetate. The benefit assessment was based on the total population of the study. For the assessment of the added benefit in the dossier [2], the pharmaceutical company (hereinafter referred to as "the company") used a subpopulation of the study that comprised patients previously treated with at least 2 vasopressors, however.

The G-BA commissioned IQWiG to assess and present the results of the subpopulation of the ATHOS-3 study based on the information provided in the dossier, taking into account the analyses submitted by the company in the commenting procedure [3]. Furthermore, the G-BA commissioned IQWiG to present the results of the outcomes "response rate of mean arterial pressure (MAP) at Hour 3" and "discontinuation of renal replacement therapy" both for the total population of the ATHOS-3 study and for the subpopulation.

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

2 Assessment

In accordance with the commission, the subpopulation of the ATHOS-3 study is assessed in the following sections. This subpopulation comprises all patients with refractory hypotension with septic or other distributive shock who were being treated with at least 2 vasopressors at the time of treatment start with the study medication. This is a subpopulation within the approved therapeutic indication of angiotensin II acetate.

2.1 Study characteristics

Detailed characteristics of the ATHOS-3 study included for the benefit assessment can be found in dossier assessment A21-95. The following sections present the study results for the subpopulation (patients previously treated with at least 2 vasopressors). The subpopulation comprises 229 patients (71.3%) of the study population of the ATHOS-3 study. These are all patients in the subpopulation who were treated with the study medication (modified intention-to-treat population, mITT). All information stated below is based on the mITT population.

Characteristics of the study population

Table 1 shows the characteristics of the patients in the subpopulation of the ATHOS-3 study.

Table 1: Characterization of the subpopulation – 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] = 114**	**Placebo + optimized standard therapy N[a] = 115**
ATHOS-3		
Age [years], mean (SD)	62 (15)	63 (15)
Sex [F/M], %	43/57	34/66
Region, n (%)		
USA/Canada	97 (85)	98 (85)
Europe	5 (4)	2 (2)
Australia/New Zealand	12 (11)	15 (13)
MAP [mmHg], mean (SD)		
At screening visit	65.5 (3.4)	64.9 (4.0)
At treatment start	66.2 (5.3)	64.7 (6.1)
$ScvO_2$ [%], mean (SD)[b]	77.2 (9.5)	77.0 (9.3)
CVP [mmHg], mean (SD)[c]	13.3 (4.6)	12.9 (4.8)
Cardiac index [L/min/m^2], mean (SD)[d]	3.3 (0.9)	3.3 (0.9)
APACHE II score at treatment start [points], mean (SD)	27.2 (8.1)	29.8 (7.9)
SOFA score at screening visit [points], mean (SD)	11.8 (2.8)	13.3 (3.2)
MELD score at treatment start [points], mean (SD)	20.9 (7.5)	23.3 (7.0)
ARDS based on X-ray findings, n (%)	25 (22)	43 (37)
Cause of distributive shock, n (%)		
Sepsis	97 (85)	100 (87)
Suspected sepsis	7 (6)	4 (4)
Vasoplegia	6 (5)	5 (4)
Pancreatitis	4 (4)	4 (4)
Other	0 (0)	2 (2)
Number of vasopressors at treatment start, n (%)		
2	81 (71[e])	83 (72[e])
3	26 (23[e])	28 (24[e])
4	7 (6[e])	4 (4[e])
Vasopressin use[f], n (%)	107 (94)	105 (91)
NED at treatment start [µg/kg/min], mean (SD)	0.47 (0.33)	0.50 (0.46)
Treatment discontinuation up to Hour 48[g, h], n (%)	47 (41)	48 (42)
Study discontinuation up to Day 7 or 3 days after completion of treatment[i], n (%)	36 (32[e])	49 (43[e])
Study discontinuation up to Day 28[j], n (%)	55 (48[e])	71 (62[e])

Table 1: Characterization of the subpopulation – 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] = 114	Placebo + optimized standard therapy N[a] = 115
a. Number of randomized patients who received the study drug (mITT). Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Information is only available for 81 vs. 77 patients in the angiotensin II and placebo arm, respectively. c. Information is only available for 86 vs. 84 patients in the angiotensin II and placebo arm, respectively. d. Information is only available for 53 vs. 58 patients in the angiotensin II and placebo arm, respectively. e. Institute's calculation. f. During the 6 hours prior to randomization. g. No information is available on the number of patients who discontinued therapy after more than 48 hours. h. Main reasons for treatment discontinuation were patient death (18 versus 28 patients) as well as MAP improvement (23 versus 10 patients). i. The main reason for study discontinuation was patient death (angiotensin II acetate: 34 patients; placebo arm: 46 patients). j. Patients who did not complete follow-up at Day 28; all of these patients died, with one exception in the placebo arm. APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: acute respiratory distress syndrome; CVP: central venous pressure; F: female; 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 Sequential Organ Failure Assessment (SOFA) score of about 12 and an Acute Physiology and Chronic Health Evaluation (APACHE) II score of about 29. In accordance with the definition of the subpopulation, all patients had been previously treated with at least 2 vasopressors. Vasopressin was used in over 90% of patients.

Risk of bias across outcomes (study level)

As described in dossier assessment A21-95, the risk of bias across outcomes is rated as low.

Transferability of the study results to the German health care context

Limited transferability of the ATHOS-3 study

A detailed description of the transferability and the limitations of the ATHOS-3 study can be found in dossier assessment A21-95. The ATHOS-3 study is an international study; of the included patients, most were from North America, and only about 10% from Europe. At 3%, the proportion of European patients in the subpopulation was lower than in the total population. As described in dossier assessment A21-95, European patients study differ markedly from the

other patients with regard to their prognosis and the therapy used. Moreover, even within Europe, different therapies are approved and standards in intensive care can vary. The results of the ATHOS-3 study are therefore transferable to the German health care context only to a limited extent.

2.2 Results

2.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - discontinuation of mechanical ventilation
  - intensive care unit (ICU) discharge
  - discontinuation of renal replacement therapy
- Health-related quality of life
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - embolic and thrombotic events (Standardized Medical Dictionary for Regulatory Activities Query [SMQ], SAEs)
  - peripheral ischaemia (Preferred Term [PT], SAEs)
  - arrhythmias
  - further specific AEs, if any

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

Table 2: Matrix of outcomes – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (subpopulation)

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, SAE)**	**Arrhythmias**	**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; ICU: intensive care unit; 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: As described in dossier assessment A21-95, the observation period of 7 days is too short for obtaining results of informative value. Hence, no usable data are available for this outcome.
- Discontinuation of renal replacement therapy: As described in dossier assessment A21-95, the observation period of 7 days is too short for obtaining results of informative value. Moreover, this is an analysis 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. Overall, no usable data are therefore available for this outcome. In accordance with the commission, the results of the outcome are presented for the subpopulation and, as supplementary information, for the total population in Appendix C.

Note on outcomes of the side effects category

- SAEs, discontinuation due to AEs and specific AEs: As described in dossier assessment A21-95, the results on side effects are interpreted as a mixture of symptoms and side effects 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. For the assessment, the results

without the exclusion of events of the SMQ of toxic-septic shock conditions are therefore used, as an isolated consideration of the AEs would not be possible even by excluding the events of the SMQ for the reasons mentioned above.

- Arrhythmias: As described in dossier assessment A21-95, the company presented analyses of so-called cardiac AEs of special interest instead of the predefined analysis of the SMQ cardiac arrhythmias and the SMQ torsade de pointes/QT prolongation. 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

In the dossier, the company presented the following analysis for the outcome of MAP response rate:

- 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.

As described in dossier assessment A21-95, the outcome of MAP response rate 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. In accordance with the commission, the results of the outcome of MAP response rate are presented for the subpopulation and, as supplementary information, for the total population in Appendix C.

2.2.2 Risk of bias

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

Table 3: Risk of bias at study and outcome levels – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (subpopulation)

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)	Arrhythmias	Further specific AEs
ATHOS-3	L	L	–[a]	L	–[a]	–[b]	L	L	L	L	–[a]	–

a. No usable data available; see Section 2.2.1 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

The risk of bias of the results of each of the included outcomes is rated as low. For the outcomes of discontinuation of mechanical ventilation, discontinuation of renal replacement therapy, and arrhythmias, no usable data are available; therefore, the risk of bias was not assessed.

Summary assessment of the certainty of conclusions

Due to limited transferability to the German health care context (see dossier assessment A21-95 and Section 2.1), the certainty of conclusions of the ATHOS-3 study is deemed limited. In addition, as described in dossier assessment A21-95, the limitations in implementation of the appropriate comparator therapy contribute to the limited certainty of conclusions.

2.2.3 Results

Table 4 and Table 5 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 were previously treated with at least 2 vasopressors (subpopulation). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The results on common AEs, SAEs and discontinuations due to AEs are presented in Appendix A. The Kaplan-Meier curves for the outcome of all-cause mortality can be found in Appendix B. The company did not provide any Kaplan-Meier curves for the outcome of ICU discharge.

Table 4: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (subpopulation)

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)	114	NA [12.8; NC] 55 (48.3)	115	11.2 [6.0; 20.5] 70 (60.9)	0.70 [0.49; 0.99]; 0.044
Morbidity					
Discontinuation of mechanical ventilation	No usable data[b]				
ICU discharge	114	15 [12; 22] 47 (41.2)	115	17 [14; 20] 42 (36.5)	0.99 [0.65; 1.50]; 0.962
Discontinuation of renal replacement therapy	No usable data[b]				
Health-related quality of life	Outcome not recorded				

a. Cox proportional hazards model and log-rank test.
b. See Section 2.2.1 for the rationale.

CI: confidence interval; HR: hazard ratio; ICU: intensive care unit; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial

Table 5: Results (side effects) – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (subpopulation)

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)	114	101 (88.6)	115	110 (95.7)	–
SAEs	114	71 (62.3)	115	84 (73.0)	0.85 [0.71; 1.02]; 0.086
Discontinuation due to AEs	114	18 (15.8)	115	32 (27.8)	0.57 [0.34; 0.95]; 0.029
Embolic and thrombotic events (SMQ, SAEs)	114	5 (4.4)	115	3 (2.6)	1.68 [0.41; 6.87]; 0.532
Peripheral ischaemia (PT, SAEs)	114	4 (3.5)	115	3 (2.6)	1.35 [0.31; 5.88]; 0.769
Arrhythmias	No usable data[c]				

a. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [4]).
b. Side effects of the intervention cannot be distinguished from symptoms of the underlying illness; see Section 2.2.1 for more information.
c. See Section 2.2.1 for a rationale.

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

Mortality

All-cause mortality (Day 28)

A statistically significant effect in favour of angiotensin II acetate + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for the outcome of all-cause mortality.

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 2.2.1).

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.

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 2.2.1).

Health-related quality of life

The ATHOS-3 study did not survey any outcomes from the health-related quality of life category.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found.

Discontinuation due to AEs

A statistically significant effect in favour of angiotensin II acetate + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for the outcome of discontinuation due to AEs.

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.

Arrhythmias

For the outcome of arrhythmias, the ATHOS-3 study provides no usable data (see Section 2.2.1).

2.2.4 Subgroups and other effect modifiers

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

- sex (male/female)

- age (< 65 years/≥ 65 years)
- APACHE II score (≤ 30 points/> 30 points)

The listed subgroup characteristics were all predefined. The company presented the corresponding subgroup analyses for the subpopulation in Module 4 A for those outcomes for which a statistically significant interaction was shown. The company presented the subgroup analyses for the remaining outcomes in Appendix 4G of its dossier without providing the interaction p-value, however.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least one 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 methods described above, the available subgroup analyses do not reveal any effect modifications.

2.3 Summary

For the subpopulation of adult patients with septic or other distributive shock who were previously treated with at least 2 vasopressors, the results from the ATHOS-3 study show overall

- a statistically significant effect in favour of angiotensin II acetate + optimized standard therapy in comparison with placebo + optimized standard therapy for the outcome of all-cause mortality, as well as
- a statistically significant effect in favour of angiotensin II acetate + optimized standard therapy in comparison with placebo + optimized standard therapy for the outcome of discontinuation due to AEs.

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Appendix A – Results on side effects (subpopulation)

The following tables present events for MedDRA System Organ Classes (SOCs) and Preferred Terms (PTs) for the overall rates of AEs and SAEs, each on the basis of the following criteria:

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

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

Table 6: Common AEs[a] – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (subpopulation)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Angiotensin II acetate + optimized standard therapy** **N = 114**	**Placebo + optimized standard therapy** **N = 115**
ATHOS-3		
Overall AE rate	101 (88.6)	110 (95.7)
Infections and infestations	33 (28.9)	25 (21.7)
Septic shock	14 (12.3)	10 (8.7)
Blood and lymphatic system disorders	23 (20.2)	20 (17.4)
Anaemia	10 (8.8)	9 (7.8)
Thrombocytopenia	13 (11.4)	8 (7.0)
Metabolic and nutritional disorders	35 (30.7)	30 (26.1)
Psychiatric disorders	14 (12.3)	8 (7.0)
Nervous system disorders	11 (9.6)	15 (13.0)
Cardiac disorders	37 (32.5)	56 (48.7)
Atrial fibrillation	12 (10.5)	14 (12.2)
Bradycardia	4 (3.5)	10 (8.7)
Vascular disorders	35 (30.7)	25 (21.7)
Hypotension	13 (11.4)	8 (7.0)
Respiratory, thoracic and mediastinal disorders	26 (22.8)	26 (22.6)
Gastrointestinal disorders	25 (21.9)	23 (20.0)
Skin and subcutaneous tissue disorders	18 (15.8)	9 (7.8)
Renal and urinary disorders	12 (10.5)	10 (8.7)
General disorders and administration site conditions	32 (28.1)	32 (27.8)
Multiple organ failure	17 (14.9)	21 (18.3)
Investigations	22 (19.3)	21 (18.3)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 18.0; SOCs and PTs taken from Module 4 A.

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

Table 7: Common SAEs[a] – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (subpopulation)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Angiotensin II acetate + optimized standard therapy** **N = 114**	**Placebo + optimized standard therapy** **N = 115**
ATHOS-3		
Overall SAE rate	71 (62.3)	84 (73.0)
Infections and infestations	22 (19.3)	18 (15.7)
Septic shock	14 (12.3)	10 (8.7)
Nervous system disorders	6 (5.3)	8 (7.0)
Cardiac disorders	19 (16.7)	29 (25.2)
Cardiac arrest	5 (4.4)	9 (7.8)
Vascular disorders	15 (13.2)	15 (13.0)
Respiratory, thoracic and mediastinal disorders	14 (12.3)	13 (11.3)
Respiratory failure	6 (5.3)	6 (5.2)
Gastrointestinal disorders	2 (1.8)	6 (5.2)
General disorders and administration site conditions	19 (16.7)	22 (19.1)
Multiple organ failure	17 (14.9)	20 (17.4)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 18.0; SOCs and PTs taken from Module 4 A.

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 8: Discontinuations due to AEs – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (subpopulation) (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Angiotensin II acetate + optimized standard therapy** **N = 114**	**Placebo + optimized standard therapy** **N = 115**
ATHOS-3		
Overall rate of discontinuations due to AEs	18 (15.8)	32 (27.8)
Infections and infestations	9 (7.9)	5 (4.3)
Peritonitis	0 (0)	1 (0.9)
Pneumonia	1 (0)	0 (0)
Sepsis	1 (0.9)	0 (0)
Septic shock	7 (6.1)	4 (3.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.9)	0 (0)
Liver cancer	1 (0.9)	0 (0)
Metabolic and nutritional disorders	0 (0)	1 (0.9)
Hyperkalaemia	0 (0)	1 (0.9)
Nervous system disorders	0 (0)	1 (0.9)
Brain oedema	0 (0)	1 (0.9)
Cardiac disorders	2 (1.8)	13 (11.3)
Bradycardia	0 (0)	1 (0.9)
Cardiac arrest	0 (0)	5 (4.3)
Cardio-respiratory arrest	0 (0)	1 (0.9)
Cardiogenic shock	1 (0.9)	4 (3.5)
Cardiopulmonary failure	1 (0.9)	0 (0)
Myocardial infarction	0 (0)	1 (0.9)
Tachycardia supraventricular	0 (0)	1 (0.9)
Vascular disorders	2 (1.8)	3 (2.6)
Circulatory collapse	0 (0)	1 (0.9)
Distributive shock	1 (0.9)	0 (0)
Hypotension	0 (0)	1 (0.9)
Peripheral ischaemia	1 (0.9)	1 (0.9)
Gastrointestinal disorders	0 (0)	2 (1.7)
Intestinal ischaemia	0 (0)	1 (0.9)
Pancreatitis	0 (0)	1 (0.9)
Hepatobiliary disorders	0 (0)	1 (0.9)
Acute hepatic failure	0 (0)	1 (0.9)
Skin and subcutaneous tissue disorders	1 (0.9)	0 (0)
Stevens Johnson syndrome	1 (0.9)	0 (0)

Table 8: Discontinuations due to AEs – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy (subpopulation) (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Angiotensin II acetate + optimized standard therapy** **N = 114**	**Placebo + optimized standard therapy** **N = 115**
General disorders and administration site conditions	4 (3.5)	6 (5.2)
Multiple organ failure	4 (3.5)	6 (5.2)

a. MedDRA version 18.0; SOCs and PTs taken from Module 4 A.

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

Appendix B – Kaplan -Meier curves on the outcome of all-cause mortality (subpopulation)

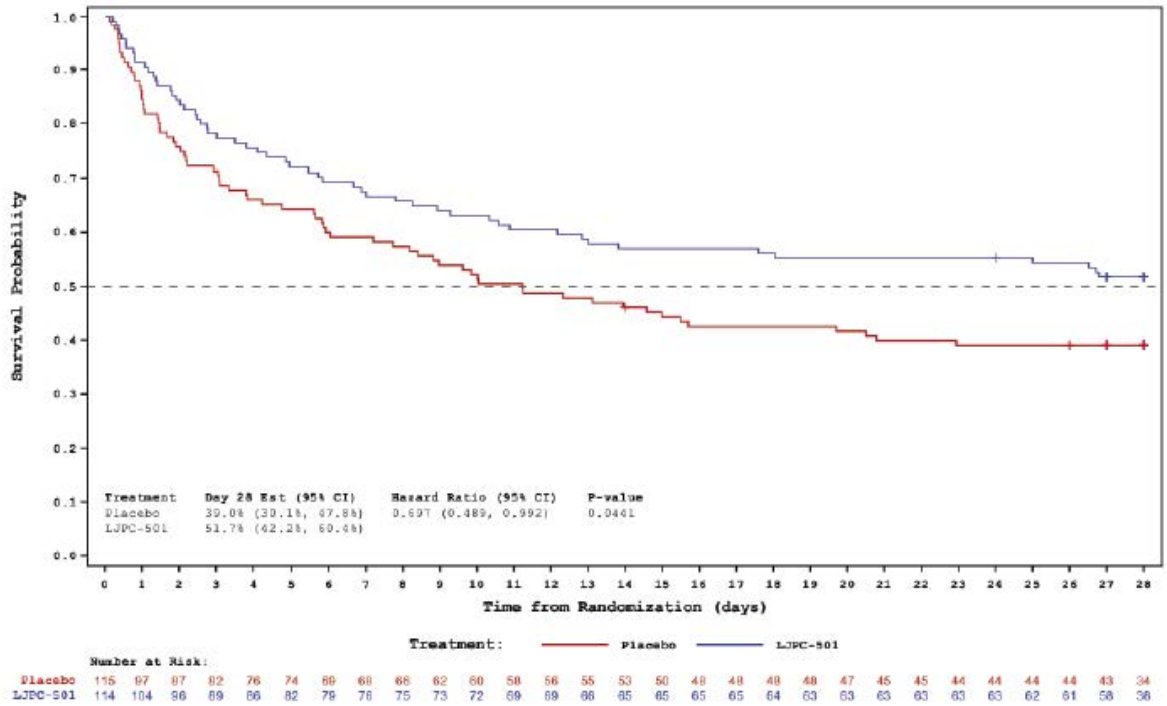

Figure 1: Kaplan-Meier curves on the outcome of all-cause mortality (subpopulation)

Appendix C – Results for the outcomes of MAP response rate and discontinuation of renal replacement therapy (total population and subpopulation) – supplementary presentation

Table 9: Results (morbidity, dichotomous, supplementary presentation) – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study Outcome category Outcome Population	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					
Morbidity					
MAP response rate 3 hours after treatment start[b]					
Total population	163	114 (69.9)	158	37 (23.4)	2.99 [2.21; 4.03]; < 0.001
Subpopulation[c]	114	76 (66.7)	115	26 (22.6)	2.95 [2.05; 4.24]; < 0.001

a. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [4]).
b. The response rate was defined as the percentage of patients who achieved a MAP ≥ 75 mmHg or MAP increase by ≥ 10 mmHg from baseline at the time point of 3 hours after treatment start.
c. Patients previously treated with at least 2 vasopressors.

CI: confidence interval; MAP: mean arterial pressure; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

Table 10: Results (morbidity, time to event, supplementary presentation) – RCT, direct comparison: angiotensin II acetate + optimized standard therapy vs. placebo + optimized standard therapy

Study **Outcome category** **Outcome** **Population**	**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					
Morbidity					
Discontinuation of renal replacement therapy[b]					
Total population	45	NA [5; NC] 17 (37.8)	60	NA 9 (15)	2.37 [1.06; 5.32]; 0.031
Subpopulation[c]	32	7 [5; NC] 12 (37.5)	52	NA 6 (11.5)	3.18 [1.19, 8.49]; 0.004

a. Cox proportional hazards model and log-rank test.
b. No analyses for the ITT population are available for this outcome. On the advice of the Food and Drug Administration, the subgroup consisting of patients with acute renal failure who had suffered acute renal failure requiring renal replacement therapy at treatment start (Hour 0) was investigated. Patients with end-stage renal failure who had previously required renal replacement therapy were excluded from the analysis. Patients were also excluded if renal replacement therapy was initiated after the start of treatment. The outcome was observed until 7 days after treatment start.
c. Patients previously treated with at least 2 vasopressors.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculated; RCT: randomized controlled trial