Clinical trial results:
Biomarker-guided implementation of angiotensin-II (AT-II) to reduce the occurrence of kidney damage after cardiac surgery

Summary

EudraCT number	2021-003088-87
Trial protocol	DE
Global end of trial date	21 March 2023

Results information

Result version number	v1 (current)
This version publication date	04 April 2024
First version publication date	04 April 2024

Trial information

Trial identification

Sponsor protocol code	WWU20_0016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05199493
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Westfälische Wilhelms-Universität
Sponsor organisation address	Schlossplatz 2, Münster, Germany, 48149 Münster
Public contact	Dept. of Anesthesiology, University Hospital Muenster, +49 02518347252, aki@anit.uni-muenster.de
Scientific contact	Dept. of Anesthesiology, University Hospital Muenster, +49 02518347252, aki@anit.uni-muenster.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2022
Global end of trial reached?	Yes
Global end of trial date	21 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to investigate the efficacy of Angiotensin-II vs. standard of care on the biomarkers [TIMP-2]*[IGFBP7] in high-risk patients undergoing cardiac surgery.

Protection of trial subjects:

All patients received standard intensive care therapy. None of the patients in both groups was exposed to additional risks. Participation in this study was voluntary. Written informed consent was obtained from patients.
This study was performed in accordance with the revision of the declaration of Helsinki (2013). Study protocol, patient information and informed consent have been submitted to the ethics comittee of the University of Münster for approval prior to trial initiation.
The treating investigator informed the patient about the nature of the trial, its aims, expected advantages as well as possible risks. Each patient had to consent in writing to participate in the study. The patient had to be given enough time and opportunity to decide on participation and to clarify any questions before the beginning of any study related procedure.
The Data Safety Monitoring Board monitored the occurrence of serious adverse events. After the session, a recommendation was made regarding the continuation of the study.

Background therapy:

The patient's primary physicians determined the remainder of patient management consistent with established best practice with the management of patients with cardiac surgery.

Evidence for comparator:

Multiple pharmacologic interventions have shown promise in animal models of AKI, however no agents have been demonstrated to be efficacious in clinical practice. As a result, the management of AKI remains primarily supportive, with CRRT serving as the cornerstone of therapy in critically ill patients with severe AKI. To investigate whether angiotensin II reduces kidney damage in patients at high risk after cardiac surgery, we will randomly assign patients at high risk for AKI identified by biomarkers to receive either angiotensin II or a 0.9 sodium chloride solution as placebo to achieve a pre-defined mean arterial pressure.

Actual start date of recruitment	01 October 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from January 2021 (First Patient In) until December 2022 and followed up until March 2023 (Last Patient out).
64 patients were enrolled and randomized to receive either Angiotensin II acetat (n=32) or control (saline) (n=32). One patient had to be excluded (drug was prepared but not administered due to his health condition)

Pre-assignment

Screening details:

419 patients were screened. 343 patients gave consent. 186 patients had no additional post-OP criterion (postoperative hypotension requiring vasopressors), 106 patients were excluded due to biomarker value < 3.7µU/ml
64 patients were randomized. One patient had to be excluded before administration of the study medication.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Labeling and blinding was performed by medical staff who are independent from the AIDED investigational team. Fluids and matching placebo were packaged in identical drug syringes. Each package contained 250 ml of fluids and was labeled with the subject identification number.

Arms

Are arms mutually exclusive?	Yes
Arm title	Angiotensin II acetat (AT II)

Arm description:

Patients randomized to the intervention group received AT-II for 12 h after randomization.

Arm type	Experimental
Investigational medicinal product name	Giapreza
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose was 20 ng/kg/min and the dose was adjusted (up to 80 ng/kg/min) so that other vasopressors could completely be weaned and the mean arterial pressure was > 65 mmHg over 12 h after randomization.

Arm title	Control

Arm description:

NaCl 0.9% after cardiac surgery

Arm type	Placebo
Investigational medicinal product name	Isotone Natriumchloridlösung 0,9 % injektionslösung
Investigational medicinal product code	
Other name	NaCl 0.9% after cardiac surgery
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The Placebo was added to the first-line vasopressor (norepinephrine) and the dose of the control

substance was adjusted so that the mean arterial pressure is above 65 mm Hg.

Number of subjects in period 1[1]	Angiotensin II acetat (AT II)	Control
Started	31	32
Completed	31	32

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient had to be excluded (drug was prepared but not administered due to his health condition)

Baseline characteristics

Reporting groups	
Reporting group title	Angiotensin II acetat (AT II)
Reporting group description:	
Patients randomized to the intervention group received AT-II for 12 h after randomization.	
Reporting group title	Control
Reporting group description:	
NaCl 0.9% after cardiac surgery	

Reporting group values	Angiotensin II acetat (AT II)	Control	Total
Number of subjects	31	32	63
Age categorical Units: Subjects			
Adults (18-64 years)	9	12	21
From 65-84 years	22	20	42
Gender categorical Units: Subjects			
Female	7	7	14
Male	24	25	49

End points

End points reporting groups	
Reporting group title	Angiotensin II acetat (AT II)
Reporting group description:	
Patients randomized to the intervention group received AT-II for 12 h after randomization.	
Reporting group title	Control
Reporting group description:	
NaCl 0.9% after cardiac surgery	

Primary: Difference of TIMP-2*IGFBP7 between time of randomization and 12 h after randomization	
End point title	Difference of TIMP-2*IGFBP7 between time of randomization and 12 h after randomization
End point description:	
End point type	Primary
End point timeframe:	
Timepoint of randomization and 12 h after randomization	

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: (ng/mL)^2/1000				
median (inter-quartile range (Q1-Q3))	0.06 (-0.24 to 0.28)	-0.08 (-0.35 to 0.14)		

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Comparison groups	Angiotensin II acetat (AT II) v Control
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Hodges-Lehmann
Parameter estimate	Location Shift
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.36

Secondary: Occurence of AKI

End point title	Occurence of AKI
End point description: Occurrence of AKI within 72h after cardiac surgery (according to the KDIGO criteria)	
End point type	Secondary
End point timeframe: within 72h after cardiac surgery	

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: Number of patients with AKI	9	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurence of moderate and severe AKI

End point title	Occurence of moderate and severe AKI
End point description: Occurrence of moderate and severe AKI within 72h after cardiac surgery (according to the KDIGO stage 2 and 3)	
End point type	Secondary
End point timeframe: within 72h after cardiac surgery	

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: No of patients with AKI stage 2/3	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Amount of study medication application

End point title	Amount of study medication application

End point description:

Total amount of study medication application within 12 h after randomization [mL]

End point type	Secondary

End point timeframe:

within 12 h after randomization

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: mL				
median (inter-quartile range (Q1-Q3))	32 (22 to 100)	259 (231 to 308)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fluid administration

End point title	Fluid administration

End point description:

End point type	Secondary

End point timeframe:

within 12 h after randomization

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: mL				
median (inter-quartile range (Q1-Q3))	2946 (2358 to 3409)	3341 (2775 to 4631)		

Statistical analyses

No statistical analyses for this end point

Secondary: Noradrenaline equivalent dose

End point title	Noradrenaline equivalent dose

End point description:

Noradrenaline equivalent dose (total amount including Noradrenalin, Adrenalin, Vasopressin, Study medication)

End point type	Secondary

End point timeframe:

During intervention (from randomization until 12 h after randomization)

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: mg				
median (inter-quartile range (Q1-Q3))	1.61 (0.81 to 3.73)	4.18 (1.40 to 6.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of vasopressor use

End point title	Duration of vasopressor use

End point description:

End point type	Secondary

End point timeframe:

During Hospital Stay

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: days				
median (inter-quartile range (Q1-Q3))	3 (2 to 4)	3.5 (2 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Creatinine clearance on day one after cardiac surgery

End point title	Creatinine clearance on day one after cardiac surgery

End point description:

End point type	Secondary

End point timeframe:

On day after cardiac surgery

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: mL/min				
median (inter-quartile range (Q1-Q3))	89.3 (67.9 to 125.4)	85.2 (64.2 to 118.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Free-days through day 28 of vasoactive drugs and mechanical ventilation

End point title	Free-days through day 28 of vasoactive drugs and mechanical ventilation

End point description:

End point type	Secondary

End point timeframe:

within 28 days after surgery

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: days				
median (inter-quartile range (Q1-Q3))	26 (25 to 27)	25.5 (22.5 to 27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal dysfunction on POD 90

End point title	Renal dysfunction on POD 90

End point description:

Patients with renal dysfunction on POD 90

End point type	Secondary

End point timeframe:
90 days after surgery

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	30		
Units: Number of patients	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: 30-day mortality

End point title	30-day mortality
End point description: Patient died before day 30	
End point type	Secondary
End point timeframe: within 30 days after surgery	

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: Number of patients	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: 60-day mortality

End point title	60-day mortality
End point description: Patient died before day 60	
End point type	Secondary
End point timeframe: within 60 days after surgery	

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: number of patients	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: 90-days mortality

End point title	90-days mortality
End point description: Patient died before day 90	
End point type	Secondary
End point timeframe: 90 days after surgery	

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	32		
Units: number of patients	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of ICU stay

End point title	Length of ICU stay
End point description:	
End point type	Secondary
End point timeframe: during primary ICU stay	

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: days				
median (inter-quartile range (Q1-Q3))	2 (1 to 8)	3.5 (1 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of hospital stay

End point title	Length of hospital stay

End point description:

End point type	Secondary

End point timeframe:
during primary hospital stay

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: days				
median (inter-quartile range (Q1-Q3))	8 (7 to 14)	8.5 (7 to 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Use of renal replacement therapy within hospital stay

End point title	Use of renal replacement therapy within hospital stay

End point description:

End point type	Secondary

End point timeframe:
during hospital stay

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: number of patients	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Use of renal replacement therapy at days 90

End point title	Use of renal replacement therapy at days 90

End point description:

End point type	Secondary

End point timeframe:

within 90 days after surgery

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: number of patients	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: MAKE90

End point title	MAKE90

End point description:

Major adverse kidney events consisting of mortality, dialysis dependency, persistent renal dysfunction (defined as serum creatinine ≥ 2x compared to baseline value at day 90)

End point type	Secondary

End point timeframe:

90 days after surgery

End point values	Angiotensin II acetat (AT II)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: number of patients	1	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events was recorded from the time the first dose of study drug was administered, up to and including follow-up-Visit d90

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Angiotensin II
Reporting group description: -	
Reporting group title	Control

Reporting group description: -

Serious adverse events	Angiotensin II	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 31 (38.71%)	15 / 32 (46.88%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemothorax			

subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	2 / 31 (6.45%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torsade de pointes			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brachial plexopathy			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebellar stroke			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Implant site infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 31 (9.68%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative wound infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Angiotensin II	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 31 (64.52%)	22 / 32 (68.75%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Meningioma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Bloody discharge			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	1 / 31 (3.23%)	2 / 32 (6.25%)	
occurrences (all)	1	3	
peripheral swelling			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
swelling			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Hypercapnia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Increased bronchial secretion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	8 / 31 (25.81%)	11 / 32 (34.38%)	
occurrences (all)	9	19	
Pneumothorax			
subjects affected / exposed	2 / 31 (6.45%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Pulmonary oedema			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Respiratory acidosis			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	4 / 31 (12.90%)	7 / 32 (21.88%)	
occurrences (all)	4	8	
Investigations			
Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Blood glucose abnormal			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
blood glucose increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Blood lactic acid increased			
subjects affected / exposed	4 / 31 (12.90%)	0 / 32 (0.00%)	
occurrences (all)	5	0	
Blood pressure decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			

subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Inflammatory marker increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Platelet count decreased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Red blood cell count decreased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	3	
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Surgical procedure repeated			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	4 / 31 (12.90%)	3 / 32 (9.38%)	
occurrences (all)	4	6	
Atrial flutter			
subjects affected / exposed	3 / 31 (9.68%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Bradycardia			
subjects affected / exposed	2 / 31 (6.45%)	4 / 32 (12.50%)	
occurrences (all)	2	4	
Cardiac failure			

subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Cardiomegaly			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	2 / 31 (6.45%)	4 / 32 (12.50%)	
occurrences (all)	2	4	
Tachyarrhythmia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	4	
Ventricular extrasystoles			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Ventricular fibrillation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Ventricular tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Brain injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	

Partial seizures			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Seizure like phenomena			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Eye disorders			
Anisocoria			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal rigidity			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	1 / 31 (3.23%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Constipation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Ulcerative gastritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	1	1	

Erythema			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Subcutaneous emphysema			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Joint warmth			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	3	
Chlamydial infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Coronavirus infection			
subjects affected / exposed	1 / 31 (3.23%)	4 / 32 (12.50%)	
occurrences (all)	1	4	
endocarditis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Klebsiella urinary tract infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Laryngopharyngitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Urinary tract infection			

subjects affected / exposed	2 / 31 (6.45%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Wound infection staphylococcal			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Hyperlactacidaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Hypervolaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Metabolic acidosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38289858