



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Two-Arm Parallel Group, Multi-Center Phase 3 Pivotal Trial to Investigate the Efficacy and Safety of Recombinant Human Alkaline Phosphatase for Treatment of Patients with Sepsis-Associated Acute Kidney Injury

Summary

EudraCT number	2019-004625-24
Trial protocol	FR NL DK FI DE GB BE IE
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	26 June 2024
First version publication date	26 June 2024

Trial information

Trial identification

Sponsor protocol code	AP-recAP-AKI-03-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04411472
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AM-Pharma B.V.
Sponsor organisation address	Stadsplateau 7, AZ Utrecht, Netherlands, 3521
Public contact	AM-Pharma Office, AM-Pharma B.V., +31 (0)30 22 89 222, office@am-pharma.com
Scientific contact	AM-Pharma Office, AM-Pharma B.V., +31 (0)30 22 89 222, office@am-pharma.com

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	Interim
Date of interim/final analysis	18 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate an effect of recombinant human alkaline phosphatase (recAP) on 28 day all cause mortality.

Protection of trial subjects:

Administration of trial drug should be stopped for any of the following reasons:

1. If in the opinion of the Investigator, an SAE indicates that continued treatment with trial drug is not in the best interest of the patient. In such cases, monitoring of the patient will continue until the event has resolved or stabilized or until a determination of a cause unrelated to the trial drug or trial procedure is made. The specific event or laboratory finding(s) must be documented in the eCRF.
2. The patient withdraws consent to receive trial drug or withdraws consent to trial participation, or the Investigator or Sponsor decide to discontinue the patient's participation in the trial.
3. After emergency unblinding of a patient.
4. The Sponsor terminates the trial.
5. Pregnancy

In case trial drug administration is discontinued prematurely, the patient should still continue all planned follow-up assessments as per protocol for safety and to allow for analysis of the specified endpoints. If trial drug administration is interrupted for any reason, re-starting of trial drug must be discussed with the Medical Monitor.

The reason for and date of trial drug discontinuation must be recorded in the eCRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2020
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	Australia: 4
Country: Number of subjects enrolled	Canada: 56
Country: Number of subjects enrolled	Japan: 33
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	United States: 52
Country: Number of subjects enrolled	Netherlands: 62
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 38
Country: Number of subjects enrolled	Denmark: 167
Country: Number of subjects enrolled	Finland: 26

Country: Number of subjects enrolled	France: 127
Country: Number of subjects enrolled	Germany: 42
Country: Number of subjects enrolled	Ireland: 6
Worldwide total number of subjects	676
EEA total number of subjects	499

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)	223
From 65 to 84 years	426
85 years and over	27

Subject disposition

Recruitment

Recruitment details:

The target patient population consist of adult patients in the intensive care unit or intermediate care unit with sepsis and new, recent onset acute kidney injury.

Pre-assignment

Screening details:

676 participants were enrolled; 21 were screening failures and were not randomized. 5 participants (2 in the active group and 3 in the placebo group) were randomized, but not been exposed to any trial drug. Consequently, 650 patients have been randomized and treated.

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, Data analyst

Blinding implementation details:

In general, all persons involved in the trial (including but not limited to the patient, site staff, the Sponsor or its designee team members) were blinded to trial drug assignment

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Main Trial Population)

Arm description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Main Trial Population: Participants with a pre-AKI reference eGFR greater than or equal to 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3

Arm title	recAP 1.6 mg/kg (Main Trial Population)
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Arm description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Main Trial Population: Participants with a pre-AKI reference eGFR greater than or equal to 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization.

Arm type	Experimental
Investigational medicinal product name	Recombinant human alkaline phosphatase (recAP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous

infusions
on Days 1, 2 and 3

Arm title	Placebo (Moderate CKD Population)
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Arm description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Moderate chronic kidney disease (CKD) Population: Participants with a pre-acute kidney injury reference estimated glomerular filtration rate more than or equal to 25 and less than 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3

Arm title	recAP 1.6 mg/kg (Moderate CKD Population)
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Arm description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions
on Days 1, 2 and 3.

Moderate chronic kidney disease (CKD) Population: Participants with a pre-acute kidney injury reference estimated glomerular filtration rate more than or equal to 25 and less than 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization.

Arm type	Active comparator
Investigational medicinal product name	Recombinant human alkaline phosphatase (recAP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions
on Days 1, 2 and 3

Arm title	Placebo (COVID-19 Population)
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Arm description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

COVID-19 Population: Participants with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury.

Arm type	Placebo
Investigational medicinal product name	Recombinant human alkaline phosphatase (recAP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions

Arm title	recAP 1.6 mg/kg (COVID-19 Population)
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Arm description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

COVID-19 Population: Participants with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury.

Arm type	Experimental
Investigational medicinal product name	Recombinant human alkaline phosphatase (recAP)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3

Number of subjects in period 1 ^[1]	Placebo (Main Trial Population)	recAP 1.6 mg/kg (Main Trial Population)	Placebo (Moderate CKD Population)
Started	277	279	31
Completed	253	248	27
Not completed	24	31	4
Physician decision	1	-	-
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	5	10	1
Study terminated by sponsor	17	20	3
Protocol deviation	1	-	-

Number of subjects in period 1 ^[1]	recAP 1.6 mg/kg (Moderate CKD Population)	Placebo (COVID-19 Population)	recAP 1.6 mg/kg (COVID-19 Population)
Started	30	13	20
Completed	29	13	20
Not completed	1	0	0
Physician decision	-	-	-
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	-	-
Study terminated by sponsor	-	-	-
Protocol deviation	-	-	-

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: 676 participants were enrolled; 21 were screening failures and were not randomized. 5 participants (2 in the active group and 3 in the placebo group) were randomized, but not been exposed to any trial drug. Consequently, 650 patients were randomized and treated.

Baseline characteristics

Reporting groups

Reporting group title	Placebo (Main Trial Population)
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Reporting group description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Main Trial Population: Participants with a pre-AKI reference eGFR greater than or equal to 45 mL/min/1.73 m²

and no proven or suspected COVID-19 at time of randomization

Reporting group title	recAP 1.6 mg/kg (Main Trial Population)
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Reporting group description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Main Trial Population: Participants with a pre-AKI reference eGFR greater than or equal to 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization.

Reporting group title	Placebo (Moderate CKD Population)
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Reporting group description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Moderate chronic kidney disease (CKD) Population: Participants with a pre-acute kidney injury reference estimated glomerular filtration rate more than or equal to 25 and less than 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization.

Reporting group title	recAP 1.6 mg/kg (Moderate CKD Population)
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Reporting group description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Moderate chronic kidney disease (CKD) Population: Participants with a pre-acute kidney injury reference estimated glomerular filtration rate more than or equal to 25 and less than 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization.

Reporting group title	Placebo (COVID-19 Population)
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Reporting group description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

COVID-19 Population: Participants with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury.

Reporting group title	recAP 1.6 mg/kg (COVID-19 Population)
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Reporting group description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

COVID-19 Population: Participants with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury.

Reporting group values	Placebo (Main Trial Population)	recAP 1.6 mg/kg (Main Trial Population)	Placebo (Moderate CKD Population)
Number of subjects	277	279	31
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	67.1 ± 12.73	68.4 ± 10.94	73.2 ± 8.90
Gender categorical Units: Subjects			
Female	104	105	8
Male	173	174	23
Race Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	23	16	0
Black or African American	9	6	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	227	233	27
Other	1	2	0
Multiple	0	1	0
Not reported	16	20	4
Missing	1	0	0
KDIGO Chronic Kidney Disease stage			
KDIGO CKD staging: 1: Normal or high (greater than or equal to 90 mL/min/1.73 min ²) 2: Mildly decreased (greater than or equal to 60 and less than 90 mL/min/1.73m ²) 3a: Mildly to moderately decreased (greater than or equal to 45 and less than 60 mL/min/1.73m ²) 3b: Moderately to severely decreased (greater than or equal to 30 and less than 45 mL/min/1.73m ²) 4: Severely decreased (greater than or equal to 15 and less than 30 mL/min/1.73m ²) 5: Kidney failure (less than 15 mL/min/1.73m ²) From KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD			
Units: Subjects			
Stage 1	67	69	4
Stage 2	152	153	6
Stage 3a	53	50	2
Stage 3b	3	7	15
Stage 4	1	0	3
Stage 5	0	0	1
Missing	1	0	0
Height			
The height and weight information was missing for one participant in the placebo group.			
Units: centimeters arithmetic mean standard deviation	170.4 ± 10.20	170.5 ± 10.30	171.2 ± 8.84
Weight			
The height and weight information was missing for one participant in the placebo group.			
Units: kilograms			

arithmetic mean	86.9	87.9	87.3
standard deviation	± 26.23	± 25.67	± 17.08
Acute Physiology and Chronic Health Evaluation II total score			
The score was not recorded for 10 participants in the placebo group and 13 participants in the recAP 1.6 mg/kg group.			
The Acute Physiology and Chronic Health Evaluation II score is a severity-of-disease classification system, used in ICU or intermediate care unit settings. A score from 0 to 71 was calculated in the eCRF from 12 physiological measurements using the worst value within the past 24 hours, age, and chronic health points (history of system organ failure). Higher scores indicate more severe disease and higher mortality risk.			
Units: Score			
arithmetic mean	23.2	23.3	25.8
standard deviation	± 7.17	± 7.65	± 7.00
Modified sequential organ failure assessment total score (eCRF)			
The score was not recorded for 1 participant in the placebo group and 3 participants in the recAP 1.6 mg/kg group.			
The Modified Sequential Organ Failure Assessment Score (mSOFA score) consists of 5 subscores (respiration, coagulation, Liver function, cardiovascular function and renal function) each ranging from 0=normal to 4=most abnormal. mSOFA is the sum of the 5 subscores (ranging from 0=normal in all subscores to 20=most abnormal in all subscores). The modified SOFA score used in the trial is exclusive of the 6th subscore (Central nervous system) from the original SOFA score.			
Units: Score			
arithmetic mean	9.4	9.1	9.5
standard deviation	± 2.52	± 2.33	± 1.46
Pre-acute kidney injury reference creatinine			
The value was not recorded for 1 participant in the placebo group.			
Units: µmol/L			
arithmetic mean	83.36	82.23	130.42
standard deviation	± 22.316	± 21.865	± 56.751
Pre-acute kidney injury reference estimated glomerular filtration rate			
The value was not recorded for 1 participant in the placebo group.			
Units: mL/min/1.73 m ²			
arithmetic mean	76.16	76.35	52.36
standard deviation	± 18.160	± 18.059	± 25.715
Acute kidney injury diagnosis creatinine			
The diagnosis was not recorded for 1 participant in the placebo group.			
Units: µmol/L			
arithmetic mean	212.43	200.06	270.10
standard deviation	± 138.656	± 123.685	± 286.051
Acute kidney injury diagnosis estimated glomerular filtration rate			
The diagnosis was not recorded for 1 participant in the placebo group.			
Units: mL/min/1.73 m ²			
arithmetic mean	32.38	33.10	25.93
standard deviation	± 14.888	± 14.958	± 12.042
Reporting group values			
	recAP 1.6 mg/kg (Moderate CKD Population)	Placebo (COVID-19 Population)	recAP 1.6 mg/kg (COVID-19 Population)
Number of subjects	30	13	20

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	70.2	68.8	62.8
standard deviation	± 11.28	± 7.67	± 10.35
Gender categorical Units: Subjects			
Female	12	2	6
Male	18	11	14
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Black or African American	1	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
White	26	11	15
Other	0	0	0
Multiple	0	0	0
Not reported	3	1	1
Missing	0	0	0
KDIGO Chronic Kidney Disease stage			
KDIGO CKD staging: 1: Normal or high (greater than or equal to 90 mL/min/1.73 min ²) 2: Mildly decreased (greater than or equal to 60 and less than 90 mL/min/1.73m ²) 3a: Mildly to moderately decreased (greater than or equal to 45 and less than 60 mL/min/1.73m ²) 3b: Moderately to severely decreased (greater than or equal to 30 and less than 45 mL/min/1.73m ²) 4: Severely decreased (greater than or equal to 15 and less than 30 mL/min/1.73m ²) 5: Kidney failure (less than 15 mL/min/1.73m ²) From KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD			
Units: Subjects			
Stage 1	2	3	3
Stage 2	9	8	13
Stage 3a	0	2	3
Stage 3b	17	0	0
Stage 4	2	0	1
Stage 5	0	0	0
Missing	0	0	0
Height			
The height and weight information was missing for one participant in the placebo group.			
Units: centimeters			
arithmetic mean	171.8	170.0	174.3

standard deviation	± 8.89	± 10.13	± 10.06
Weight			
The height and weight information was missing for one participant in the placebo group.			
Units: kilograms			
arithmetic mean	86.5	98.9	87.1
standard deviation	± 16.94	± 26.67	± 19.39
Acute Physiology and Chronic Health Evaluation II total score			
The score was not recorded for 10 participants in the placebo group and 13 participants in the recAP 1.6 mg/kg group.			
The Acute Physiology and Chronic Health Evaluation II score is a severity-of-disease classification system, used in ICU or intermediate care unit settings. A score from 0 to 71 was calculated in the eCRF from 12 physiological measurements using the worst value within the past 24 hours, age, and chronic health points (history of system organ failure). Higher scores indicate more severe disease and higher mortality risk.			
Units: Score			
arithmetic mean	23.6	23.1	23.6
standard deviation	± 5.77	± 6.87	± 8.31
Modified sequential organ failure assessment total score (eCRF)			
The score was not recorded for 1 participant in the placebo group and 3 participants in the recAP 1.6 mg/kg group.			
The Modified Sequential Organ Failure Assessment Score (mSOFA score) consists of 5 subscores (respiration, coagulation, Liver function, cardiovascular function and renal function) each ranging from 0=normal to 4=most abnormal. mSOFA is the sum of the 5 subscores (ranging from 0=normal in all subscores to 20=most abnormal in all subscores). The modified SOFA score used in the trial is exclusive of the 6th subscore (Central nervous system) from the original SOFA score.			
Units: Score			
arithmetic mean	9.0	9.4	9.6
standard deviation	± 1.88	± 1.66	± 2.030
Pre-acute kidney injury reference creatinine			
The value was not recorded for 1 participant in the placebo group.			
Units: µmol/L			
arithmetic mean	122.56	87.99	95.97
standard deviation	± 33.684	± 23.494	± 27.159
Pre-acute kidney injury reference estimated glomerular filtration rate			
The value was not recorded for 1 participant in the placebo group.			
Units: mL/min/1.73 m²			
arithmetic mean	51.57	74.88	72.82
standard deviation	± 21.945	± 15.742	± 18.438
Acute kidney injury diagnosis creatinine			
The diagnosis was not recorded for 1 participant in the placebo group.			
Units: µmol/L			
arithmetic mean	210.11	176.20	211.30
standard deviation	± 93.540	± 42.570	± 148.803
Acute kidney injury diagnosis estimated glomerular filtration rate			
The diagnosis was not recorded for 1 participant in the placebo group.			
Units: mL/min/1.73 m²			
arithmetic mean	30.97	33.54	35.42
standard deviation	± 20.116	± 7.002	± 16.461
Reporting group values	Total		

Number of subjects	650		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	237		
Male	413		
Race			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	41		
Black or African American	19		
Native Hawaiian or Other Pacific Islander	0		
White	539		
Other	3		
Multiple	1		
Not reported	45		
Missing	1		
KDIGO Chronic Kidney Disease stage			
KDIGO CKD staging: 1: Normal or high (greater than or equal to 90 mL/min/1.73 min ²) 2: Mildly decreased (greater than or equal to 60 and less than 90 mL/min/1.73m ²) 3a: Mildly to moderately decreased (greater than or equal to 45 and less than 60 mL/min/1.73m ²) 3b: Moderately to severely decreased (greater than or equal to 30 and less than 45 mL/min/1.73m ²) 4: Severely decreased (greater than or equal to 15 and less than 30 mL/min/1.73m ²) 5: Kidney failure (less than 15 mL/min/1.73m ²) From KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD			
Units: Subjects			
Stage 1	148		
Stage 2	341		
Stage 3a	110		
Stage 3b	42		
Stage 4	7		
Stage 5	1		
Missing	1		

Height			
The height and weight information was missing for one participant in the placebo group.			
Units: centimeters arithmetic mean standard deviation	-		
Weight			
The height and weight information was missing for one participant in the placebo group.			
Units: kilograms arithmetic mean standard deviation	-		
Acute Physiology and Chronic Health Evaluation II total score			
The score was not recorded for 10 participants in the placebo group and 13 participants in the recAP 1.6 mg/kg group.			
The Acute Physiology and Chronic Health Evaluation II score is a severity-of-disease classification system, used in ICU or intermediate care unit settings. A score from 0 to 71 was calculated in the eCRF from 12 physiological measurements using the worst value within the past 24 hours, age, and chronic health points (history of system organ failure). Higher scores indicate more severe disease and higher mortality risk.			
Units: Score arithmetic mean standard deviation	-		
Modified sequential organ failure assessment total score (eCRF)			
The score was not recorded for 1 participant in the placebo group and 3 participants in the recAP 1.6 mg/kg group.			
The Modified Sequential Organ Failure Assessment Score (mSOFA score) consists of 5 subscores (respiration, coagulation, Liver function, cardiovascular function and renal function) each ranging from 0=normal to 4=most abnormal. mSOFA is the sum of the 5 subscores (ranging from 0=normal in all subscores to 20=most abnormal in all subscores). The modified SOFA score used in the trial is exclusive of the 6th subscore (Central nervous system) from the original SOFA score.			
Units: Score arithmetic mean standard deviation	-		
Pre-acute kidney injury reference creatinine			
The value was not recorded for 1 participant in the placebo group.			
Units: µmol/L arithmetic mean standard deviation	-		
Pre-acute kidney injury reference estimated glomerular filtration rate			
The value was not recorded for 1 participant in the placebo group.			
Units: mL/min/1.73 m ² arithmetic mean standard deviation	-		
Acute kidney injury diagnosis creatinine			
The diagnosis was not recorded for 1 participant in the placebo group.			
Units: µmol/L arithmetic mean standard deviation	-		
Acute kidney injury diagnosis estimated glomerular filtration rate			
The diagnosis was not recorded for 1 participant in the placebo group.			
Units: mL/min/1.73 m ²			

arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo (Main Trial Population)
Reporting group description:	
Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.	
Main Trial Population: Participants with a pre-AKI reference eGFR greater than or equal to 45 mL/min/1.73 m ² and no proven or suspected COVID-19 at time of randomization	
Reporting group title	recAP 1.6 mg/kg (Main Trial Population)
Reporting group description:	
Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.	
Main Trial Population: Participants with a pre-AKI reference eGFR greater than or equal to 45 mL/min/1.73 m ² and no proven or suspected COVID-19 at time of randomization.	
Reporting group title	Placebo (Moderate CKD Population)
Reporting group description:	
Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.	
Moderate chronic kidney disease (CKD) Population: Participants with a pre-acute kidney injury reference estimated glomerular filtration rate more than or equal to 25 and less than 45 mL/min/1.73 m ² and no proven or suspected COVID-19 at time of randomization.	
Reporting group title	recAP 1.6 mg/kg (Moderate CKD Population)
Reporting group description:	
Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.	
Moderate chronic kidney disease (CKD) Population: Participants with a pre-acute kidney injury reference estimated glomerular filtration rate more than or equal to 25 and less than 45 mL/min/1.73 m ² and no proven or suspected COVID-19 at time of randomization.	
Reporting group title	Placebo (COVID-19 Population)
Reporting group description:	
Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.	
COVID-19 Population: Participants with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury.	
Reporting group title	recAP 1.6 mg/kg (COVID-19 Population)
Reporting group description:	
Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.	
COVID-19 Population: Participants with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury.	
Subject analysis set title	Placebo: Moderate Chronic Kidney Disease Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with a pre-acute kidney injury reference estimated glomerular filtration rate ≥ 25 and < 45 mL/min/1.73 m ² and no proven or suspected COVID-19 at time of randomization	
Subject analysis set title	recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with a pre-acute kidney injury reference estimated glomerular filtration rate ≥ 25 and < 45 mL/min/1.73 m ² and no proven or suspected COVID-19 at time of randomization	
Subject analysis set title	Placebo: COVID-19 Population

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury	
Subject analysis set title	recAP 1.6 mg/kg: COVID-19 Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury	
Subject analysis set title	Placebo: Combined Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Combined population: From the 650 patients in the mITT population (321 Placebo and 329 recAP), 649 were analysed in the combined population (1 participant randomized and treated with placebo has been excluded as no efficacy data were available). In the combined population participants were analyzed as treated, resulting in 319 Placebo and 330 recAP participants (2 participants randomized to Placebo were treated with recAP, 1 participant randomized to recAP was treated with placebo).	
Subject analysis set title	recAP 1.6 mg/kg: Combined Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Combined population: From the 650 patients in the mITT population (321 Placebo and 329 recAP), 649 were analysed in the combined population (1 participant randomized and treated with placebo has been excluded as no efficacy data were available). In the combined population participants were analyzed as treated, resulting in 319 Placebo and 330 recAP participants (2 participants randomized to Placebo were treated with recAP, 1 participant randomized to recAP was treated with placebo).	

Primary: 28-day All-cause Mortality: Main Trial Population

End point title	28-day All-cause Mortality: Main Trial Population ^[1]
End point description:	
To demonstrate an effect of recAP on 28 day all cause mortality	
End point type	Primary
End point timeframe:	
28 days	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This analysis is only of the main trial population. See the Subject Disposition section for the full population description.

End point values	Placebo (Main Trial Population)	recAP 1.6 mg/kg (Main Trial Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	279		
Units: participants				
Participants with known survival status at Day 28	272	279		
Number of participants died by Day 28	69	80		
Survival status is unknown at Day 28	5	0		

Statistical analyses

Statistical analysis title	28-day All-cause Mortality: Main Trial Population
Comparison groups	Placebo (Main Trial Population) v recAP 1.6 mg/kg (Main Trial Population)
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8025
Method	One-sided p-value
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.805
upper limit	1.732

Primary: 28-day All-cause Mortality: Moderate Chronic Kidney Disease Population

End point title	28-day All-cause Mortality: Moderate Chronic Kidney Disease Population
End point description:	To demonstrate an effect of recAP on 28 day all cause mortality
End point type	Primary
End point timeframe:	28 days

End point values	Placebo: Moderate Chronic Kidney Disease Population	recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: participants				
Participants with known survival status at Day 28	31	29		
Number of participants died by Day 28	10	6		
Survival status is unknown at Day 28	0	1		

Statistical analyses

Statistical analysis title	28-day All-cause Mortality: Moderate Chronic Kidne
Comparison groups	Placebo: Moderate Chronic Kidney Disease Population v recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1824
Method	One-sided p-value
Parameter estimate	Odds ratio (OR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.139
upper limit	2.131

Primary: 28-day All-cause Mortality: COVID-19 Population

End point title	28-day All-cause Mortality: COVID-19 Population
End point description:	To demonstrate an effect of recAP on 28 day all cause mortality
End point type	Primary
End point timeframe:	28 days

End point values	Placebo: COVID-19 Population	recAP 1.6 mg/kg: COVID- 19 Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	20		
Units: participants				
Participants with known survival status at Day 28	13	20		
Number of participants died by Day 28	11	5		
Survival status is unknown at Day 28	0	0		

Statistical analyses

Statistical analysis title	28-day All-cause Mortality: COVID-19 Population
Comparison groups	Placebo: COVID-19 Population v recAP 1.6 mg/kg: COVID-19 Population
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	One-sided p-value
Parameter estimate	Odds ratio (OR)
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.405

Secondary: Major Adverse Kidney Events 90: Main Trial Population

End point title	Major Adverse Kidney Events 90: Main Trial Population ^[2]
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End point description:

Major adverse kidney events (MAKE) 90: dead by Day 90 or on Renal Replacement Therapy (RRT) at Day 90 or greater than or equal to 25% decline in estimated glomerular filtration rate (eGFR) on both Day 28 and Day 90 relative to the known or assumed pre-acute kidney injury reference level.

MAKE 90 eGFR Decline = MAKE 90: greater than or equal to 25% decline in eGFR rate on both Day 28 and Day 90

End point type	Secondary
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End point timeframe:

90 days

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This analysis is only of the main trial population. See the Subject Disposition section for the full population description.

End point values	Placebo (Main Trial Population)	recAP 1.6 mg/kg (Main Trial Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	279		
Units: participants				
Participants with missing data on MAKE 90	36	49		
Participants with unknown data on MAKE 90	46	34		
MAKE 90: Dead	89	97		
MAKE 90: On RRT	2	0		
MAKE 90 eGFR Decline	15	7		

Statistical analyses

Statistical analysis title	Main Trial Population
Comparison groups	Placebo (Main Trial Population) v recAP 1.6 mg/kg (Main Trial Population)
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3894
Method	One-sided p-value
Parameter estimate	Odds ratio (OR)
Point estimate	0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.606
upper limit	1.454

Secondary: Major Adverse Kidney Events 90: Moderate Chronic Kidney Disease Population

End point title	Major Adverse Kidney Events 90: Moderate Chronic Kidney Disease Population
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End point description:

Major adverse kidney events (MAKE) 90: dead by Day 90 or on Renal Replacement Therapy (RRT) at Day 90 or greater than or equal to 25% decline in estimated glomerular filtration rate (eGFR) on both Day 28 and Day 90 relative to the known or assumed pre-acute kidney injury reference level.

MAKE 90 eGFR Decline = MAKE 90: greater than or equal to 25% decline in eGFR rate on both Day 28 and Day 90

End point type	Secondary
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End point timeframe:

90 days

End point values	Placebo: Moderate Chronic Kidney Disease Population	recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: participants				
Participants with missing data on MAKE 90	7	7		
Participants with unknown data on MAKE 90	2	6		
MAKE 90: Dead	13	7		
MAKE 90: On RRT	0	0		
MAKE 90 eGFR Decline	1	1		

Statistical analyses

Statistical analysis title	MAKE 90: Moderate Chronic Kidney Disease Population
Comparison groups	Placebo: Moderate Chronic Kidney Disease Population v recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1237
Method	One-sided p-value
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.128
upper limit	1.697

Secondary: Major Adverse Kidney Events 90: COVID-19 Population

End point title	Major Adverse Kidney Events 90: COVID-19 Population
End point description:	
Major adverse kidney events (MAKE) 90: dead by Day 90 or on Renal Replacement Therapy (RRT) at Day 90 or greater than or equal to 25% decline in estimated glomerular filtration rate (eGFR) on both Day 28 and Day 90 relative to the known or assumed pre-acute kidney injury reference level.	
MAKE 90 eGFR Decline = MAKE 90: greater than or equal to 25% decline in eGFR rate on both Day 28 and Day 90	
End point type	Secondary
End point timeframe:	
90 days	

End point values	Placebo: COVID-19 Population	recAP 1.6 mg/kg: COVID- 19 Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	20		
Units: participants				
Participants with missing data on MAKE 90	1	4		
Participants with unknown data on MAKE 90	0	0		
MAKE 90: Dead	11	6		
MAKE 90: On RRT	0	0		
MAKE 90 eGFR Decline	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Days Alive and Free of Organ Support Through Day 28: Main Trial Population

End point title	Days Alive and Free of Organ Support Through Day 28: Main Trial Population ^[3]
End point description: Days alive and free of organ support through Day 28, ie, days alive with no mechanical ventilation (MV), Renal Replacement Therapy (RRT), vasopressors, or inotropes (with death within 28 days counting as zero days)	
End point type	Secondary
End point timeframe: 28 days	
Notes: [3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This analysis is only of the main trial population. See the Subject Disposition section for the full population description.	

End point values	Placebo (Main Trial Population)	recAP 1.6 mg/kg (Main Trial Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	279		
Units: days				
arithmetic mean (standard deviation)				
Alive and free of organ support	13.2 (± 11.33)	12.8 (± 11.34)		
Number of days free of MV	14.7 (± 11.93)	14.3 (± 12.19)		
Number of days free of RRT	18.4 (± 12.40)	17.9 (± 12.64)		
Number of days free of vasopressors and inotropes	16.5 (± 10.85)	15.9 (± 11.17)		

Statistical analyses

Statistical analysis title	Days Alive and Free of Organ Support
Statistical analysis description: Days Alive and Free of Organ Support Through Day 28: Main Trial Population	
Comparison groups	recAP 1.6 mg/kg (Main Trial Population) v Placebo (Main Trial Population)
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546 ^[4]
Method	One-sided p-value
Notes: [4] - One-sided p-value from re-randomization test	

Statistical analysis title	Number of days free of MV
Statistical analysis description: Days Alive and Free of Organ Support Through Day 28: Main Trial Population	
Comparison groups	Placebo (Main Trial Population) v recAP 1.6 mg/kg (Main Trial Population)

Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.677 ^[5]
Method	One-sided p-value

Notes:

[5] - One-sided p-value from re-randomization test

Statistical analysis title	Number of days free of RRT
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Statistical analysis description:

Days Alive and Free of Organ Support Through Day 28: Main Trial Population

Comparison groups	Placebo (Main Trial Population) v recAP 1.6 mg/kg (Main Trial Population)
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.993 ^[6]
Method	One-sided p-value

Notes:

[6] - One-sided p-value from re-randomization test

Statistical analysis title	Number of days free of vasopressors and inotropes
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Statistical analysis description:

Days Alive and Free of Organ Support Through Day 28: Main Trial Population

Comparison groups	Placebo (Main Trial Population) v recAP 1.6 mg/kg (Main Trial Population)
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.779 ^[7]
Method	One-sided p-value

Notes:

[7] - One-sided p-value from re-randomization test

Secondary: Days Alive and Free of Organ Support Through Day 28: Moderate Chronic Kidney Disease Population

End point title	Days Alive and Free of Organ Support Through Day 28: Moderate Chronic Kidney Disease Population
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End point description:

Days alive and free of organ support through Day 28, ie, days alive with no mechanical ventilation (MV), Renal Replacement Therapy (RRT), vasopressors, or inotropes (with death within 28 days counting as zero days)

End point type	Secondary
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End point timeframe:

28 days

End point values	Placebo: Moderate Chronic Kidney Disease Population	recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: days				
arithmetic mean (standard deviation)				
Alive and free of organ support	10.5 (± 10.59)	17.2 (± 10.30)		
Number of days free of MV	11.2 (± 11.47)	18.1 (± 11.11)		
Number of days free of RRT	17.8 (± 12.81)	21.4 (± 11.71)		
Number of days free of vasopressors and inotropes	14.8 (± 11.15)	19.4 (± 10.58)		

Statistical analyses

Statistical analysis title	Days alive and free of organ support
Comparison groups	Placebo: Moderate Chronic Kidney Disease Population v recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051 ^[8]
Method	One-sided p-value

Notes:

[8] - One-sided p-value from re-randomization test

Statistical analysis title	Number of days free of MV
Comparison groups	recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population v Placebo: Moderate Chronic Kidney Disease Population
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 ^[9]
Method	One-sided p-value

Notes:

[9] - One-sided p-value from re-randomization test

Statistical analysis title	Number of days free of RRT
Comparison groups	Placebo: Moderate Chronic Kidney Disease Population v recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025 ^[10]
Method	One-sided p-value

Notes:

[10] - One-sided p-value from re-randomization test

Statistical analysis title	Number of days free of vasopressors and inotropes
Comparison groups	Placebo: Moderate Chronic Kidney Disease Population v recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073 ^[11]
Method	One-sided p-value

Notes:

[11] - One-sided p-value from re-randomization test

Secondary: Days Alive and Free of Organ Support Through Day 28: COVID-19 Population

End point title	Days Alive and Free of Organ Support Through Day 28: COVID-19 Population
End point description: Days alive and free of organ support through Day 28, ie, days alive with no mechanical ventilation (MV), Renal Replacement Therapy (RRT), vasopressors, or inotropes (with death within 28 days counting as zero days)	
End point type	Secondary
End point timeframe: 28 days	

End point values	Placebo: COVID-19 Population	recAP 1.6 mg/kg: COVID-19 Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	20		
Units: days				
arithmetic mean (standard deviation)				
Alive and free of organ support	1.5 (± 5.27)	8.3 (± 10.24)		
Number of days free of MV	3.3 (± 8.14)	8.6 (± 10.85)		
Number of days free of RRT	2.3 (± 7.74)	19.7 (± 13.09)		
Number of days free of vasopressors and inotropes	3.6 (± 8.83)	14.9 (± 11.29)		

Statistical analyses

Statistical analysis title	Alive and free of organ support through Day 28
Comparison groups	Placebo: COVID-19 Population v recAP 1.6 mg/kg: COVID-19 Population

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 ^[12]
Method	One-sided p-value

Notes:

[12] - One-sided p-value from re-randomization test

Statistical analysis title	Number of days free of MV
Comparison groups	Placebo: COVID-19 Population v recAP 1.6 mg/kg: COVID-19 Population
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.979 ^[13]
Method	One-sided p-value

Notes:

[13] - One-sided p-value from re-randomization test

Statistical analysis title	Number of days free of RRT
Comparison groups	Placebo: COVID-19 Population v recAP 1.6 mg/kg: COVID-19 Population
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.675 ^[14]
Method	One-sided p-value

Notes:

[14] - One-sided p-value from re-randomization test

Statistical analysis title	Number of days free of vasopressors and inotropes
Comparison groups	Placebo: COVID-19 Population v recAP 1.6 mg/kg: COVID-19 Population
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031 ^[15]
Method	One-sided p-value

Notes:

[15] - One-sided p-value from re-randomization test

Secondary: Days Alive and Out of the ICU Through Day 28: Main Trial Population

End point title	Days Alive and Out of the ICU Through Day 28: Main Trial Population ^[16]
End point description:	Days alive and out of the ICU through Day 28 (with death within 28 days counting as zero days).
End point type	Secondary
End point timeframe:	28 days

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis is only of the main trial population. See the Subject Disposition section for the full population description.

End point values	Placebo (Main Trial Population)	recAP 1.6 mg/kg (Main Trial Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	279		
Units: days				
arithmetic mean (standard deviation)				
Alive and Out of the ICU	11.4 (± 10.56)	11.4 (± 10.42)		

Statistical analyses

Statistical analysis title	Days Alive and Out of the ICU
Comparison groups	Placebo (Main Trial Population) v recAP 1.6 mg/kg (Main Trial Population)
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.545 ^[17]
Method	One-sided p-value

Notes:

[17] - One-sided p-value from re-randomization test

Secondary: Days Alive and Out of the ICU Through Day 28: Moderate Chronic Kidney Disease Population

End point title	Days Alive and Out of the ICU Through Day 28: Moderate Chronic Kidney Disease Population
End point description:	Days alive and out of the ICU through Day 28 (with death within 28 days counting as zero days).
End point type	Secondary
End point timeframe:	28 days

End point values	Placebo: Moderate Chronic Kidney Disease Population	recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: days				
arithmetic mean (standard deviation)				

Alive and Out of the ICU	8.1 (\pm 9.60)	14.7 (\pm 10.09)		
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Statistical analyses

Statistical analysis title	Days Alive and Out of the ICU
Comparison groups	Placebo: Moderate Chronic Kidney Disease Population v recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081 ^[18]
Method	One-sided p-value

Notes:

[18] - One-sided p-value from re-randomization test

Secondary: Days Alive and Out of the ICU Through Day 28: COVID-19 Population

End point title	Days Alive and Out of the ICU Through Day 28: COVID-19 Population
End point description:	Days alive and out of the ICU through Day 28 (with death within 28 days counting as zero days).
End point type	Secondary
End point timeframe:	28 days

End point values	Placebo: COVID-19 Population	recAP 1.6 mg/kg: COVID-19 Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	20		
Units: days				
arithmetic mean (standard deviation)				
Alive and Out of the ICU	3.0 (\pm 7.39)	7.5 (\pm 9.60)		

Statistical analyses

Statistical analysis title	Days Alive and Out of the ICU
Comparison groups	Placebo: COVID-19 Population v recAP 1.6 mg/kg: COVID-19 Population

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.979 ^[19]
Method	One-sided p-value

Notes:

[19] - One-sided p-value from re-randomization test

Secondary: 90-day All Cause Mortality: Main Trial Population

End point title	90-day All Cause Mortality: Main Trial Population ^[20]
End point description:	
90-Day all-cause mortality	
End point type	Secondary
End point timeframe:	
28 days	

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This analysis is only of the main trial population. See the Subject Disposition section for the full population description.

End point values	Placebo (Main Trial Population)	recAP 1.6 mg/kg (Main Trial Population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	279		
Units: participants				
Participants with event	89	97		
Participants censored	188	182		

Statistical analyses

Statistical analysis title	90-day All Cause Mortality
Comparison groups	recAP 1.6 mg/kg (Main Trial Population) v Placebo (Main Trial Population)
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6916
Method	One-sided p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.806
upper limit	1.437

Secondary: 90-day All Cause Mortality: Moderate Chronic Kidney Disease Population

End point title	90-day All Cause Mortality: Moderate Chronic Kidney Disease Population
End point description: 90-Day all-cause mortality	
End point type	Secondary
End point timeframe: 90 days	

End point values	Placebo: Moderate Chronic Kidney Disease Population	recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	30		
Units: participants				
Participants with event	13	7		
Participants censored	18	23		

Statistical analyses

Statistical analysis title	90-day All Cause Mortality
Comparison groups	Placebo: Moderate Chronic Kidney Disease Population v recAP 1.6 mg/kg: Moderate Chronic Kidney Disease Population
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0628
Method	One-sided p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	1.234

Secondary: 90-day All Cause Mortality: COVID-19 Population

End point title	90-day All Cause Mortality: COVID-19 Population
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End point description:	
90-Day all-cause mortality	
End point type	Secondary
End point timeframe:	
90 days	

End point values	Placebo: COVID-19 Population	recAP 1.6 mg/kg: COVID- 19 Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	20		
Units: participants				
Participants with event	11	6		
Participants censored	2	14		

Statistical analyses

Statistical analysis title	90-day All Cause Mortality
Comparison groups	Placebo: COVID-19 Population v recAP 1.6 mg/kg: COVID-19 Population
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	One-sided p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.054

Secondary: Major Adverse Kidney Events Through Day 90: Combined Population

End point title	Major Adverse Kidney Events Through Day 90: Combined Population
End point description:	
Major Adverse Kidney Events through day 90 (MAKE90A) : death until day 90, greater than 25% drop in estimated glomerular filtration rate at Day 90, on renal replacement therapy (RRT) at day 90 OR on RRT through Day 28.	
Combined population.	
End point type	Secondary
End point timeframe:	
90 days	

End point values	Placebo: Combined Population	recAP 1.6 mg/kg: Combined Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	319	330		
Units: Participants				
MAKE90A	206	187		
Death until day 90	111	112		
Greater than 25% drop in eGFR at Day 90 visit	28	19		
On RRT at Day 90 visit OR on RRT through day 28	116	93		
Rehospitalization	30	28		

Statistical analyses

Statistical analysis title	Combined Population
Comparison groups	recAP 1.6 mg/kg: Combined Population v Placebo: Combined Population
Number of subjects included in analysis	649
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 ^[21]
Method	one-sided p-value
Parameter estimate	z-score statistic difference proportions
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	-0.4

Notes:

[21] - one-sided p-value based on the z-score statistic for the difference in proportions

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were followed to D28. Ongoing SAEs on D28 were followed up until resolution (up to D180). SAEs starting after D28 were to be reported if at least possibly related to study drug. Mortality status was collected up to D180, or premature termination.

Adverse event reporting additional description:

In the safety population participants were analyzed according to the treatment received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Placebo (Main Trial Safety Population, n=276))
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Reporting group description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Reporting group title	recAP 1.6 mg/kg (Main Trial Safety Population, n=280)
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Reporting group description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Reporting group title	Placebo (Moderate CKD Trial Safety Population, n=31)
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Reporting group description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

Moderate chronic kidney disease (CKD) Population: Participants with a pre-acute kidney injury reference estimated glomerular filtration rate more than or equal to 25 and less than 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization

Reporting group title	recAP 1.6 mg/kg (Moderate CKD Safety Population, n=30)
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Reporting group description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3

Moderate chronic kidney disease (CKD) Population: Participants with a pre-acute kidney injury reference estimated glomerular filtration rate more than or equal to 25 and less than 45 mL/min/1.73 m² and no proven or suspected COVID-19 at time of randomization

Reporting group title	Placebo (Covid 19 Safety Population, n=13)
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Reporting group description:

Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

COVID-19 Population: Participants with proven or suspected COVID-19 at time of randomization with or without

'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury

Reporting group title	recAP 1.6 mg/kg (Covid 19 Safety Population, n=20)
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Reporting group description:

Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.

COVID-19 Population: Participants with proven or suspected COVID-19 at time of randomization with or without 'moderate' chronic kidney disease and, for patients in this population, COVID-19 should have been the main cause of sepsis-associated acute kidney injury

Serious adverse events	Placebo (Main Trial Safety Population, n=276))	recAP 1.6 mg/kg (Main Trial Safety Population, n=280)	Placebo (Moderate CKD Trial Safety Population, n=31)
Total subjects affected by serious adverse events			
subjects affected / exposed	112 / 276 (40.58%)	125 / 280 (44.64%)	18 / 31 (58.06%)
number of deaths (all causes)	92	108	14
number of deaths resulting from adverse events	76	87	11
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastatic neoplasm			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Plasmablastic lymphoma			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 276 (0.00%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	2 / 276 (0.72%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 1	0 / 0
Shock haemorrhagic			

subjects affected / exposed	2 / 276 (0.72%)	3 / 280 (1.07%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypovolaemic shock			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Deep vein thrombosis			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	12 / 276 (4.35%)	16 / 280 (5.71%)	3 / 31 (9.68%)
occurrences causally related to treatment / all	0 / 12	2 / 16	0 / 3
deaths causally related to treatment / all	0 / 12	2 / 16	0 / 3
Hernia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Death			
subjects affected / exposed	0 / 276 (0.00%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	15 / 276 (5.43%)	15 / 280 (5.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 15	2 / 15	0 / 0
deaths causally related to treatment / all	0 / 6	2 / 11	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 276 (0.36%)	4 / 280 (1.43%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 276 (0.00%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Aspiration			
subjects affected / exposed	0 / 276 (0.00%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 276 (0.00%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Hypoxia			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	3 / 276 (1.09%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizoaffective disorder			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Craniocerebral injury			

subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Drain site complication			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fascial rupture			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wound dehiscence			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic leak			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			

subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	7 / 276 (2.54%)	6 / 280 (2.14%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 8	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 5	1 / 4	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 276 (0.72%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Right ventricular failure			
subjects affected / exposed	1 / 276 (0.36%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	2 / 276 (0.72%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Myocarditis			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulseless electrical activity			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Torsade de pointes			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	2 / 276 (0.72%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 276 (0.72%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	2 / 276 (0.72%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	2 / 276 (0.72%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Papillary muscle rupture			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyarrhythmia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			

subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 276 (0.36%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cerebellar infarction			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serotonin syndrome			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 276 (0.00%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Intensive care unit acquired weakness			

subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Neuromyopathy			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	4 / 276 (1.45%)	7 / 280 (2.50%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 4	3 / 7	0 / 0
deaths causally related to treatment / all	0 / 3	3 / 6	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 276 (0.72%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Ileus paralytic			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Large intestine perforation			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric venous occlusion			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haemorrhage			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ischaemia			

subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 276 (0.72%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal fluid collection			
subjects affected / exposed	2 / 276 (0.72%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising oesophagitis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal fistula			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic mass			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			

subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 276 (0.36%)	3 / 280 (1.07%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 1
Hepatorenal failure			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatorenal syndrome			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	3 / 276 (1.09%)	4 / 280 (1.43%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nephropathy toxic			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Soft tissue disorder			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Septic shock			
subjects affected / exposed	21 / 276 (7.61%)	16 / 280 (5.71%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	3 / 21	1 / 16	0 / 2
deaths causally related to treatment / all	3 / 17	1 / 12	0 / 2
Pneumonia			
subjects affected / exposed	5 / 276 (1.81%)	8 / 280 (2.86%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 5	1 / 10	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 0

Sepsis			
subjects affected / exposed	3 / 276 (1.09%)	3 / 280 (1.07%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest wall abscess			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex encephalitis			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infection			

subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 276 (0.36%)	2 / 280 (0.71%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Purulent pericarditis			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis infective			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fungaemia			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex pneumonia			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural abscess			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising soft tissue infection			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			

subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal abscess			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspergillus infection			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperphosphataemia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Serious adverse events	recAP 1.6 mg/kg	Placebo (Covid 19)	recAP 1.6 mg/kg
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	(Moderate CKD Safety Population, n=30)	Safety Population, n=13)	(Covid 19 Safety Population, n=20)
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 30 (36.67%)	11 / 13 (84.62%)	7 / 20 (35.00%)
number of deaths (all causes)	7	11	7
number of deaths resulting from adverse events	7	11	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasmablastic lymphoma			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			

subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 30 (3.33%)	1 / 13 (7.69%)	2 / 20 (10.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 2
Hernia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 30 (3.33%)	5 / 13 (38.46%)	2 / 20 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 5	0 / 2
Pulmonary embolism			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 30 (0.00%)	2 / 13 (15.38%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Aspiration			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoxia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizoaffective disorder			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Craniocerebral injury			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drain site complication			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fascial rupture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wound dehiscence			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic leak			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulseless electrical activity			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Torsade de pointes			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary muscle rupture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	2 / 20 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyarrhythmia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			

subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serotonin syndrome			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intensive care unit acquired weakness			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuromyopathy			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ileus paralytic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric venous occlusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ischaemia			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising oesophagitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal fistula			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic mass			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatorenal failure			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal syndrome			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Soft tissue disorder			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest wall abscess			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex encephalitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purulent pericarditis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis infective			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex pneumonia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural abscess			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising soft tissue infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal abscess			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspergillus infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperphosphataemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo (Main Trial Safety Population, n=276))	recAP 1.6 mg/kg (Main Trial Safety Population, n=280)	Placebo (Moderate CKD Trial Safety Population, n=31)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 276 (51.45%)	131 / 280 (46.79%)	18 / 31 (58.06%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 276 (2.54%)	6 / 280 (2.14%)	0 / 31 (0.00%)
occurrences (all)	7	6	0
Jugular vein thrombosis			
subjects affected / exposed	2 / 276 (0.72%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
Haemodynamic instability			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Ileostomy			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Toe amputation			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 276 (3.99%)	5 / 280 (1.79%)	0 / 31 (0.00%)
occurrences (all)	12	6	0
Asthenia			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Hyperthermia			
subjects affected / exposed	3 / 276 (1.09%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0

Oedema peripheral subjects affected / exposed occurrences (all)	3 / 276 (1.09%) 3	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Reproductive system and breast disorders Postmenopausal haemorrhage subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all)	8 / 276 (2.90%) 8	5 / 280 (1.79%) 5	2 / 31 (6.45%) 2
Atelectasis subjects affected / exposed occurrences (all)	3 / 276 (1.09%) 3	3 / 280 (1.07%) 3	0 / 31 (0.00%) 0
Pulmonary oedema subjects affected / exposed occurrences (all)	2 / 276 (0.72%) 2	3 / 280 (1.07%) 3	0 / 31 (0.00%) 0
Respiratory failure subjects affected / exposed occurrences (all)	4 / 276 (1.45%) 4	2 / 280 (0.71%) 2	0 / 31 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	1 / 280 (0.36%) 1	0 / 31 (0.00%) 0
Pneumothorax subjects affected / exposed occurrences (all)	3 / 276 (1.09%) 3	1 / 280 (0.36%) 1	0 / 31 (0.00%) 0
Respiratory acidosis subjects affected / exposed occurrences (all)	1 / 276 (0.36%) 1	0 / 280 (0.00%) 0	1 / 31 (3.23%) 1
Pharyngeal swelling subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	1 / 31 (3.23%) 1
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	5 / 276 (1.81%) 5	10 / 280 (3.57%) 10	2 / 31 (6.45%) 2

Delirium			
subjects affected / exposed	12 / 276 (4.35%)	8 / 280 (2.86%)	1 / 31 (3.23%)
occurrences (all)	13	10	1
Anxiety			
subjects affected / exposed	0 / 276 (0.00%)	4 / 280 (1.43%)	1 / 31 (3.23%)
occurrences (all)	0	4	1
Agitation			
subjects affected / exposed	3 / 276 (1.09%)	3 / 280 (1.07%)	0 / 31 (0.00%)
occurrences (all)	3	3	0
Insomnia			
subjects affected / exposed	1 / 276 (0.36%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Investigations			
Lipase increased			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Transaminases increased			
subjects affected / exposed	2 / 276 (0.72%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	2	0	1
Gastric residual increased			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	3 / 276 (1.09%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences (all)	3	2	0
Enterococcus test positive			
subjects affected / exposed	2 / 276 (0.72%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Blood lactic acid increased			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Post procedural haemorrhage subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Stoma site haemorrhage subjects affected / exposed occurrences (all)	1 / 276 (0.36%) 1	2 / 280 (0.71%) 2	1 / 31 (3.23%) 1
Vascular pseudoaneurysm subjects affected / exposed occurrences (all)	1 / 276 (0.36%) 1	1 / 280 (0.36%) 1	1 / 31 (3.23%) 1
Anastomotic leak subjects affected / exposed occurrences (all)	1 / 276 (0.36%) 1	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Wound dehiscence subjects affected / exposed occurrences (all)	3 / 276 (1.09%) 3	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	22 / 276 (7.97%) 23	26 / 280 (9.29%) 28	2 / 31 (6.45%) 3
Atrial flutter subjects affected / exposed occurrences (all)	2 / 276 (0.72%) 2	5 / 280 (1.79%) 5	1 / 31 (3.23%) 1
Supraventricular tachycardia subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	3 / 280 (1.07%) 3	0 / 31 (0.00%) 0
Bradycardia subjects affected / exposed occurrences (all)	2 / 276 (0.72%) 2	1 / 280 (0.36%) 1	1 / 31 (3.23%) 1
Aortic valve incompetence subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Ventricular tachycardia subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	1 / 31 (3.23%) 1
Myocardial ischaemia			

subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Nervous system disorders			
Psychomotor hyperactivity			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Encephalopathy			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Intensive care unit acquired weakness			
subjects affected / exposed	4 / 276 (1.45%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	4	0	1
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Ischaemic stroke			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Loss of consciousness			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences (all)	0	1	2
Cerebral ischaemia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 276 (5.80%)	26 / 280 (9.29%)	2 / 31 (6.45%)
occurrences (all)	17	26	2
Thrombocytopenia			

subjects affected / exposed	13 / 276 (4.71%)	12 / 280 (4.29%)	1 / 31 (3.23%)
occurrences (all)	14	12	1
Coagulopathy			
subjects affected / exposed	2 / 276 (0.72%)	5 / 280 (1.79%)	1 / 31 (3.23%)
occurrences (all)	2	5	1
Leukocytosis			
subjects affected / exposed	4 / 276 (1.45%)	3 / 280 (1.07%)	1 / 31 (3.23%)
occurrences (all)	4	3	1
Leukopenia			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 276 (3.26%)	10 / 280 (3.57%)	0 / 31 (0.00%)
occurrences (all)	9	10	0
Constipation			
subjects affected / exposed	5 / 276 (1.81%)	3 / 280 (1.07%)	0 / 31 (0.00%)
occurrences (all)	5	3	0
Dysphagia			
subjects affected / exposed	2 / 276 (0.72%)	3 / 280 (1.07%)	0 / 31 (0.00%)
occurrences (all)	3	3	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 276 (0.72%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences (all)	2	2	0
Rectal haemorrhage			
subjects affected / exposed	2 / 276 (0.72%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences (all)	2	2	0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	1 / 31 (3.23%)
occurrences (all)	1	1	1
Ileus paralytic			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Pancreatic fistula			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1

Ulcerative gastritis subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	1 / 31 (3.23%) 1
Gastritis subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Lower gastrointestinal haemorrhage subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer subjects affected / exposed occurrences (all)	3 / 276 (1.09%) 3	8 / 280 (2.86%) 8	0 / 31 (0.00%) 0
Drug eruption subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	1 / 280 (0.36%) 1	1 / 31 (3.23%) 1
Toxic skin eruption subjects affected / exposed occurrences (all)	1 / 276 (0.36%) 1	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Skin discolouration subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Skin lesion subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	3 / 280 (1.07%) 3	0 / 31 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Haematoma muscle subjects affected / exposed occurrences (all)	0 / 276 (0.00%) 0	0 / 280 (0.00%) 0	0 / 31 (0.00%) 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	10 / 276 (3.62%)	4 / 280 (1.43%)	1 / 31 (3.23%)
occurrences (all)	11	5	1
Urinary tract infection			
subjects affected / exposed	3 / 276 (1.09%)	3 / 280 (1.07%)	1 / 31 (3.23%)
occurrences (all)	3	3	1
Abdominal abscess			
subjects affected / exposed	0 / 276 (0.00%)	2 / 280 (0.71%)	1 / 31 (3.23%)
occurrences (all)	0	2	1
Candida infection			
subjects affected / exposed	1 / 276 (0.36%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Peritonitis			
subjects affected / exposed	0 / 276 (0.00%)	2 / 280 (0.71%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 276 (0.00%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Septic shock			
subjects affected / exposed	1 / 276 (0.36%)	1 / 280 (0.36%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Herpes simplex			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Penile infection			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Abdominal wall infection			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Pneumonia bacterial			

subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Enterococcal infection			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Endocarditis			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Infectious pleural effusion			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	2 / 276 (0.72%)	3 / 280 (1.07%)	0 / 31 (0.00%)
occurrences (all)	2	3	0
Pneumonia klebsiella			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Tinea cruris			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	12 / 276 (4.35%)	15 / 280 (5.36%)	1 / 31 (3.23%)
occurrences (all)	13	15	1
Hypernatraemia			
subjects affected / exposed	9 / 276 (3.26%)	11 / 280 (3.93%)	0 / 31 (0.00%)
occurrences (all)	9	11	0
Hyperkalaemia			
subjects affected / exposed	3 / 276 (1.09%)	8 / 280 (2.86%)	0 / 31 (0.00%)
occurrences (all)	4	8	0
Hypophosphataemia			
subjects affected / exposed	5 / 276 (1.81%)	7 / 280 (2.50%)	0 / 31 (0.00%)
occurrences (all)	5	7	0
Fluid overload			
subjects affected / exposed	3 / 276 (1.09%)	4 / 280 (1.43%)	1 / 31 (3.23%)
occurrences (all)	3	4	2

Hyperglycaemia			
subjects affected / exposed	3 / 276 (1.09%)	4 / 280 (1.43%)	1 / 31 (3.23%)
occurrences (all)	4	4	1
Acidosis			
subjects affected / exposed	1 / 276 (0.36%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Lactic acidosis			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 276 (0.00%)	0 / 280 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	recAP 1.6 mg/kg (Moderate CKD Safety Population, n=30)	Placebo (Covid 19 Safety Population, n=13)	recAP 1.6 mg/kg (Covid 19 Safety Population, n=20)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 30 (43.33%)	5 / 13 (38.46%)	12 / 20 (60.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Jugular vein thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Haemodynamic instability			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Ileostomy			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

Toe amputation subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1
Asthenia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Hyperthermia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 13 (7.69%) 1	0 / 20 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	2 / 20 (10.00%) 2
Reproductive system and breast disorders			
Postmenopausal haemorrhage subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 13 (7.69%) 1	0 / 20 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Atelectasis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Pulmonary oedema subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Respiratory failure subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1
Epistaxis			

subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Pneumothorax subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 2
Respiratory acidosis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Pharyngeal swelling subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Psychiatric disorders			
Confusional state subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Delirium subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Agitation subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1
Insomnia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1
Investigations			
Lipase increased subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Oxygen saturation decreased subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Transaminases increased			

subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Gastric residual increased subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1
Enterococcus test positive subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 13 (7.69%) 1	0 / 20 (0.00%) 0
Blood lactic acid increased subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Stoma site haemorrhage subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Vascular pseudoaneurysm subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Anastomotic leak subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 13 (7.69%) 1	0 / 20 (0.00%) 0
Wound dehiscence subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 13 (7.69%) 1	0 / 20 (0.00%) 0
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3	0 / 13 (0.00%) 0	3 / 20 (15.00%) 3
Atrial flutter			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Bradycardia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Aortic valve incompetence			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Ventricular tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 13 (15.38%)	1 / 20 (5.00%)
occurrences (all)	0	4	1
Myocardial ischaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Psychomotor hyperactivity			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Taste disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Encephalopathy			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Intensive care unit acquired weakness			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ischaemic cerebral infarction			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ischaemic stroke			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Loss of consciousness			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cerebral ischaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Coagulopathy			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Dysphagia			

subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ileus paralytic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pancreatic fistula			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ulcerative gastritis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Drug eruption			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Toxic skin eruption			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

Skin discolouration subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Skin lesion subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 13 (7.69%) 1	0 / 20 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Musculoskeletal and connective tissue disorders Haematoma muscle subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Abdominal abscess subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Candida infection subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 13 (0.00%) 0	0 / 20 (0.00%) 0
Peritonitis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 13 (7.69%) 1	0 / 20 (0.00%) 0
Escherichia urinary tract infection subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1
Oral herpes subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 13 (0.00%) 0	1 / 20 (5.00%) 1

Septic shock			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Penile infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Abdominal wall infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pneumonia bacterial			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Enterococcal infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Endocarditis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Infectious pleural effusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pneumonia klebsiella			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tinea cruris			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences (all)	0	1	0

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hypernatraemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 13 (7.69%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Fluid overload			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Acidosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Lactic acidosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 30 (0.00%)	0 / 13 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2020	<p>Austria and Germany:</p> <ul style="list-style-type: none">• Addition of country-specific exclusion criterion to exclude patients with legally confirmed permanent mental incapacity and an appointed legal guardian for trial protocol version 1
07 September 2020	<p>United Kingdom:</p> <ul style="list-style-type: none">• Exclusion criterion 12 (use of nonmarketed drugs) was updated to further clarify exclusion as requested by the MHRA• Addition of the country-specific definition of women of childbearing potential
15 January 2021	<p>Japan:</p> <ul style="list-style-type: none">• Addition of a country-specific exclusion criterion regarding patients who have a known allergy or intolerance to any component of recAP• Addition of the definition of women of childbearing potential according to country-specific regulatory guidance
25 October 2021	<ul style="list-style-type: none">• Definitions of MAKE 90 and MAKE 28 endpoints were clarified• COVID-19 population further specified (ie, COVID-19 should have been main cause of SA-AKI)• Overall trial design was updated to include an estimate of treatment effect and to describe the additional exploratory analyses• Exclusion criterion 17 (ie, eGFR cut-off) was revised to account for variation in clinical practice and regulations, correcting for race• Additional sites in Japan and Australia were added• An additional biomarker blood sample was added to Day 28• The option for a longer follow-up of ADA was included and maximum trial duration was adjusted accordingly• Criteria for stopping drug administration were updated to include the emergency unblinding of a patient• The option to use registries, depending on local regulations, to obtain survival data were added• The definition of women of childbearing potential was added• A section for assessment of 12-lead electrocardiogram was added• A description of sample collection during home visits was added• The recording of RRT status was extended to Day 90• Sensitivity analyses for the MAKE 90 and time to death through to Day 90 endpoints were added• SAE recording was updated to only collect SAEs and not also deaths up to Day 180• Other revisions throughout for improved clarity of text and minor revisions for consistency
02 December 2021	<p>Japan: Removal of the previous country-specific definition of women of childbearing potential since trial protocol amendment 01 included this information.</p>
16 December 2021	<p>United Kingdom:</p> <ul style="list-style-type: none">• Removal of the country-specific definition of women of childbearing potential since trial protocol amendment 01 included this information

22 December 2021	Germany: <ul style="list-style-type: none">• Remote Source Data Verification monitoring may be temporarily allowed due to COVID-19 pandemic
20 January 2022	Austria and Germany: <ul style="list-style-type: none">• Addition of country-specific exclusion criterion to exclude patients with legally confirmed permanent mental incapacity and an appointed legal guardian for trial protocol version 2
05 April 2022	Denmark: <ul style="list-style-type: none">• Remote Source Data Verification monitoring may be temporarily allowed due to COVID-19 pandemic

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 August 2022	The trial was terminated early due to futility being reached for the primary endpoint of all cause mortality at day 28 at the interim analysis.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was terminated early due to futility being reached for the primary endpoint of all cause mortality at day 28 at the interim analysis.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37012016>

<http://www.ncbi.nlm.nih.gov/pubmed/38172296>