# 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 |

**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) |

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) |
|---|---|

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) |
|---|---|

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) |
|---|---|

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

on Days 1, 2 and 3

| **Arm title** | recAP 1.6 mg/kg (COVID-19 Population) |
|---|---|

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) |
| Reporting group description: | |
| Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.<br><br>Main Trial Population: Participants with a pre-AKI reference eGFR greater than or equal to 45 mL/min/1.73 m2<br>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.<br><br>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) |
| Reporting group description: | |
| Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.<br><br>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) |
| Reporting group description: | |
| Recombinant human alkaline phosphatase (recAP) 1.6mg/kg; 3 daily 1-hour continuous intravenous infusions<br>on Days 1, 2 and 3.<br><br>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) |
| Reporting group description: | |
| Matching placebo; 3 daily 1-hour continuous intravenous infusions on Days 1, 2 and 3.<br><br>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.<br><br>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<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |

| | | | |
|---|---|---|---|
| Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 67.1 | 68.4 | 73.2 |
| standard deviation | ± 12.73 | ± 10.94 | ± 8.90 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 104 | 105 | 8 |
| Male | 173 | 174 | 23 |
| Race<br>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:<br>1: Normal or high (greater than or equal to 90 mL/min/1.73 min^2)<br>2: Mildly decreased (greater than or equal to 60 and less than 90 mL/min/1.73m^2)<br>3a: Mildly to moderately decreased (greater than or equal to 45 and less than 60 mL/min/1.73m^2)<br>3b: Moderately to severely decreased (greater than or equal to 30 and less than 45 mL/min/1.73m^2)<br>4: Severely decreased (greater than or equal to 15 and less than 30 mL/min/1.73m^2)<br>5: Kidney failure (less than 15 mL/min/1.73m^2)<br><br>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 | 170.4 | 170.5 | 171.2 |
| standard deviation | ± 10.20 | ± 10.30 | ± 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.<br><br>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.<br><br>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 m² | | | |
| 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 m² | | | |
| 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<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 70.2 | 68.8 | 62.8 |
| standard deviation | ± 11.28 | ± 7.67 | ± 10.35 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 12 | 2 | 6 |
| Male | 18 | 11 | 14 |
| Race<br>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:<br>1: Normal or high (greater than or equal to 90 mL/min/1.73 min^2)<br>2: Mildly decreased (greater than or equal to 60 and less than 90 mL/min/1.73m^2)<br>3a: Mildly to moderately decreased (greater than or equal to 45 and less than 60 mL/min/1.73m^2)<br>3b: Moderately to severely decreased (greater than or equal to 30 and less than 45 mL/min/1.73m^2)<br>4: Severely decreased (greater than or equal to 15 and less than 30 mL/min/1.73m^2)<br>5: Kidney failure (less than 15 mL/min/1.73m^2)<br><br>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.<br><br>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.<br><br>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<br>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<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 237 | | |
| Male | 413 | | |
| Race<br>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:<br>1: Normal or high (greater than or equal to 90 mL/min/1.73 min^2)<br>2: Mildly decreased (greater than or equal to 60 and less than 90 mL/min/1.73m^2)<br>3a: Mildly to moderately decreased (greater than or equal to 45 and less than 60 mL/min/1.73m^2)<br>3b: Moderately to severely decreased (greater than or equal to 30 and less than 45 mL/min/1.73m^2)<br>4: Severely decreased (greater than or equal to 15 and less than 30 mL/min/1.73m^2)<br>5: Kidney failure (less than 15 mL/min/1.73m^2)<br><br>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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Weight | | | |
| The height and weight information was missing for one participant in the placebo group. | | | |
| Units: kilograms<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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.<br><br>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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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.<br><br>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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Pre-acute kidney injury reference creatinine | | | |
| The value was not recorded for 1 participant in the placebo group. | | | |
| Units: µmol/L<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Acute kidney injury diagnosis creatinine | | | |
| The diagnosis was not recorded for 1 participant in the placebo group. | | | |
| Units: µmol/L<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>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 m2
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 m2 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 m2 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 m2 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 m2 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 m2 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:<br>To demonstrate an effect of recAP on 28 day all cause mortality | |
| End point type | Primary |
| End point timeframe:<br>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] |
|---|---|

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

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 |
|---|---|

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: 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 |
|---|---|

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 |
|---|---|

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 |

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: 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 (± 9.60) | 14.7 (± 10.09) | | |

**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 (± 7.39) | 7.5 (± 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:<br>90-Day all-cause mortality | |
| End point type | Secondary |
| End point timeframe:<br>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 |

| | |
|---|---|
| End point description:<br>90-Day all-cause mortality | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo (Main Trial Safety Population, n=276)) |

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) |

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) |

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) |

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) |

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) |

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 |
|---|---|---|---|

| | (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 | 3 / 276 (1.09%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 8 / 276 (2.90%) | 5 / 280 (1.79%) | 2 / 31 (6.45%) |
| occurrences (all) | 8 | 5 | 2 |
| Atelectasis | | | |
| subjects affected / exposed | 3 / 276 (1.09%) | 3 / 280 (1.07%) | 0 / 31 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 2 / 276 (0.72%) | 3 / 280 (1.07%) | 0 / 31 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 4 / 276 (1.45%) | 2 / 280 (0.71%) | 0 / 31 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 280 (0.36%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 276 (1.09%) | 1 / 280 (0.36%) | 0 / 31 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 280 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Pharyngeal swelling | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 5 / 276 (1.81%) | 10 / 280 (3.57%) | 2 / 31 (6.45%) |
| occurrences (all) | 5 | 10 | 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 | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 2 / 280 (0.71%) | 1 / 31 (3.23%) |
| occurrences (all) | 1 | 2 | 1 |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 1 / 280 (0.36%) | 1 / 31 (3.23%) |
| occurrences (all) | 1 | 1 | 1 |
| Anastomotic leak | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wound dehiscence | | | |
| subjects affected / exposed | 3 / 276 (1.09%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 22 / 276 (7.97%) | 26 / 280 (9.29%) | 2 / 31 (6.45%) |
| occurrences (all) | 23 | 28 | 3 |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 276 (0.72%) | 5 / 280 (1.79%) | 1 / 31 (3.23%) |
| occurrences (all) | 2 | 5 | 1 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 3 / 280 (1.07%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Bradycardia | | | |
| subjects affected / exposed | 2 / 276 (0.72%) | 1 / 280 (0.36%) | 1 / 31 (3.23%) |
| occurrences (all) | 2 | 1 | 1 |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 0 | 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 | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 3 / 276 (1.09%) | 8 / 280 (2.86%) | 0 / 31 (0.00%) |
| occurrences (all) | 3 | 8 | 0 |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 1 / 280 (0.36%) | 1 / 31 (3.23%) |
| occurrences (all) | 0 | 1 | 1 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 1 / 276 (0.36%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 3 / 280 (1.07%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Haematoma muscle | | | |
| subjects affected / exposed | 0 / 276 (0.00%) | 0 / 280 (0.00%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 0 | 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 | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 13 (7.69%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Reproductive system and breast disorders | | | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 13 (7.69%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Epistaxis | | | |

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastric residual increased | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Enterococcus test positive | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 13 (7.69%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood lactic acid increased | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anastomotic leak | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 13 (7.69%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 13 (7.69%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 30 (10.00%) | 0 / 13 (0.00%) | 3 / 20 (15.00%) |
| occurrences (all) | 3 | 0 | 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 | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 13 (7.69%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Haematoma muscle | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 13 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 13 (7.69%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 13 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 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 | Austria and Germany:<br><br>• 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 | United Kingdom:<br><br>• Exclusion criterion 12 (use of nonmarketed drugs) was updated to further clarify exclusion as requested by the<br>MHRA<br>• Addition of the country-specific definition of women of childbearing potential |
| 15 January 2021 | Japan:<br><br>• Addition of a country-specific exclusion criterion regarding patients who have a known allergy or intolerance to any<br>component of recAP<br>• Addition of the definition of women of childbearing potential according to country-specific regulatory guidance |
| 25 October 2021 | • Definitions of MAKE 90 and MAKE 28 endpoints were clarified<br>• COVID-19 population further specified (ie, COVID-19 should have been main cause of SA-AKI)<br>• Overall trial design was updated to include an estimate oftreatment effect and to describe the additional exploratory analyses<br>• Exclusion criterion 17 (ie, eGRF cut-off) was revised to account for variation in clinical practice and regulations, correcting for race<br>• Additional sites in Japan and Australia were added<br>• An additional biomarker blood sample was added to Day 28<br>• The option for a longer follow-up of ADA was included and maximum trial duration was adjusted accordingly<br>• Criteria for stopping drug administration were updated to include the emergency unblinding of a patient<br>• The option to use registries, depending on local regulations, to obtain survival data were added<br>• The definition of women of childbearing potential was added<br>• A section for assessment of 12-lead electrocardiogram was added<br>• A description of sample collection during home visits was added<br>• The recording of RRT status was extended to Day 90<br>• Sensitivity analyses for the MAKE 90 and time to death through to Day 90 endpoints were added<br>• SAE recording was updated to only collect SAEs and not also deaths up to Day 180<br>• Other revisions throughout for improved clarity of text and minor revisions for consistency |
| 02 December 2021 | Japan: Removal of the previous country-specific definition of women of childbearing potential since trial protocol amendment 01 included this information. |
| 16 December 2021 | United Kingdom:<br><br>• Removal of the country-specific definition of women of childbearing potential since trial protocol amendment 01<br>included this information |

| | |
|---|---|
| 22 December 2021 | Germany:<br><br>• Remote Source Data Verification monitoring may be temporarily allowed due to COVID-19 pandemic |
| 20 January 2022 | Austria and Germany:<br><br>• Addition of country-specific exclusion criterion to exclude patients with legally confirmed permanent mental<br>incapacity and an appointed legal guardian for trial protocol version 2 |
| 05 April 2022 | Denmark:<br><br>• 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