# Clinical trial results:
# A Prospective, Randomised, Double-blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia

## Summary

| | |
|---|---|
| EudraCT number | 2012-002862-11 |
| Trial protocol | GB EE DE BE LV CZ HU SK AT GR PT HR IT |
| Global end of trial date | 06 June 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 30 May 2019 |
| First version publication date | 30 May 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 7625A-008 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02070757 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck Registration: MK-7625A-008 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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 | Final |
| Date of interim/final analysis | 06 June 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 May 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 June 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This is a phase 3, multicenter, prospective, randomised study of intravenous (IV) ceftolozane/tazobactam versus IV meropenem in the treatment of adult participants with either ventilator associated bacterial pneumonia (VABP) or ventilated hospital-acquired bacterial pneumonia (HABP). The primary objective is to demonstrate the noninferiority of ceftolozane/tazobactam versus meropenem in adult participants with ventilated nosocomial pneumonia (VNP) based on the difference in Day 28 all-cause mortality rates in the Intent-to-treat (ITT) population using a non-inferiority margin of 10%.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 September 2014 |
| 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: 9 |
| Country: Number of subjects enrolled | Japan: 13 |
| Country: Number of subjects enrolled | New Zealand: 1 |
| Country: Number of subjects enrolled | Philippines: 31 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 1 |
| Country: Number of subjects enrolled | Taiwan: 2 |
| Country: Number of subjects enrolled | Croatia: 6 |
| Country: Number of subjects enrolled | Czech Republic: 83 |
| Country: Number of subjects enrolled | Estonia: 48 |
| Country: Number of subjects enrolled | Georgia: 58 |
| Country: Number of subjects enrolled | Hungary: 6 |
| Country: Number of subjects enrolled | Latvia: 3 |
| Country: Number of subjects enrolled | Russian Federation: 176 |
| Country: Number of subjects enrolled | Serbia: 13 |
| Country: Number of subjects enrolled | Ukraine: 70 |
| Country: Number of subjects enrolled | Brazil: 33 |
| Country: Number of subjects enrolled | Colombia: 1 |

| | |
|---|---|
| Country: Number of subjects enrolled | Guatemala: 8 |
| Country: Number of subjects enrolled | United States: 31 |
| Country: Number of subjects enrolled | Israel: 13 |
| Country: Number of subjects enrolled | Lebanon: 3 |
| Country: Number of subjects enrolled | South Africa: 12 |
| Country: Number of subjects enrolled | Belgium: 20 |
| Country: Number of subjects enrolled | France: 50 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Ireland: 4 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Portugal: 1 |
| Country: Number of subjects enrolled | Spain: 16 |
| Worldwide total number of subjects | 726 |
| EEA total number of subjects | 251 |

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) | 406 |
| From 65 to 84 years | 289 |
| 85 years and over | 31 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 263 sites were opened for enrollment with the majority of participants recruited from sites in eastern Europe.

### Pre-assignment

Screening details:

Participants enrolled in the study were at least 18 years of age with ventilated nosocomial pneumonia (VNP). Participants were eligible to participate in the study if they met all of the inclusion criteria and none of the exclusion criteria at the screening visit.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ceftolozane/Tazobactam |

Arm description:

Participants receive 3000 mg ceftolozane/tazobactam (comprising 2000 mg ceftolozane and 1000 mg tazobactam) administered as an IV infusion every 8 hours (q8h).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ceftolozane/Tazobactam |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

3000 mg (2000 mg ceftolozane and 1000 mg tazobactam) every 8 hours (q8h) for 8-14 days.

| | |
|---|---|
| **Arm title** | Meropenem |

Arm description:

Participants receive 1000 mg meropenem administered as an IV infusion q8h.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Meropenem |
| Investigational medicinal product code | |
| Other name | MERREM® |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

1000 mg meropenem every 8 hours (q8h) for 8-14 days.

| **Number of subjects in period 1** | Ceftolozane/Tazobactam | Meropenem |
|---|---|---|
| Started | 362 | 364 |
| Treated Participants | 361 | 359 |
| Completed | 245 | 250 |
| Not completed | 117 | 114 |
| Discharged from Study Hospital | 2 | 2 |
| Consent withdrawn by subject | 1 | 3 |
| Adverse Event (including fatal) | 107 | 99 |
| Investigator Decision | - | 2 |
| Lost to follow-up | 7 | 4 |
| Protocol deviation | - | 4 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ceftolozane/Tazobactam |
| Reporting group description: | |
| Participants receive 3000 mg ceftolozane/tazobactam (comprising 2000 mg ceftolozane and 1000 mg tazobactam) administered as an IV infusion every 8 hours (q8h). | |
| Reporting group title | Meropenem |
| Reporting group description: | |
| Participants receive 1000 mg meropenem administered as an IV infusion q8h. | |

| Reporting group values | Ceftolozane/Tazobactam | Meropenem | Total |
|---|---|---|---|
| Number of subjects | 362 | 364 | 726 |
| Age Categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 202 | 204 | 406 |
| From 65-84 years | 144 | 145 | 289 |
| 85 years and over | 16 | 15 | 31 |
| Gender Categorical<br>Units: Subjects | | | |
| Male | 262 | 255 | 517 |
| Female | 100 | 109 | 209 |

## End points

### End points reporting groups

| Reporting group title | Ceftolozane/Tazobactam |
|---|---|
| Reporting group description: | |
| Participants receive 3000 mg ceftolozane/tazobactam (comprising 2000 mg ceftolozane and 1000 mg tazobactam) administered as an IV infusion every 8 hours (q8h). | |
| Reporting group title | Meropenem |
| Reporting group description: | |
| Participants receive 1000 mg meropenem administered as an IV infusion q8h. | |

### Primary: Percentage of Participants with a Clinical Response of Clinical Cure at the Test-of-Cure (TOC) Visit in the Intent-to-Treat (ITT) Population

| End point title | Percentage of Participants with a Clinical Response of Clinical Cure at the Test-of-Cure (TOC) Visit in the Intent-to-Treat (ITT) Population |
|---|---|
| End point description: | |
| To demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult participants with ventilated nosocomial pneumonia (VNP) at the TOC visit (7 to 14 days after the end-of-therapy [EOT] visit) using a non-inferiority margin of 12.5%. Clinical response at the TOC visit was defined as cure (complete resolution with no new signs of VNP), failure (progression, relapse or recurrence of VNP) or indeterminate (no evaluable study data). A favorable clinical response is a clinical cure. A missing clinical response will be considered indeterminate unless the clinical outcome at the EOT visit was failure.The estimated adjusted percentage was a weighted average across all strata, constructed using Mehrotra-Railkar continuity-corrected minimum risk (MRc) stratum weights. The ITT population consisted of all randomized participants with documented informed consent, regardless of whether or not they received study drug. | |
| End point type | Primary |
| End point timeframe: | |
| 7 to 14 days after last dose of study drug (Up to ~Day 30) | |

| End point values | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 362 | 364 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 97.5%) | 54.4 (48.74 to 60.30) | 53.3 (47.72 to 59.25) | | |

### Statistical analyses

| Statistical analysis title | Ceftolozane/Tazobactam vs. Meropenem |
|---|---|
| Statistical analysis description: | |
| The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (ventilator-associated bacterial pneumonia [VABP] or ventilated hospital-acquired bacterial pneumonia [HABP]) and age (<65, >= 65) categories. The 97.5% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference. | |

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |
| Number of subjects included in analysis | 726 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Difference in percentage of participants |
| Point estimate | 1.1 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -7.2 |
| upper limit | 9.31 |

## Secondary: Percentage of Participants with All Cause Mortality in the Intent-to-Treat (ITT) Population - Day 28

| | |
|---|---|
| End point title | Percentage of Participants with All Cause Mortality in the Intent-to-Treat (ITT) Population - Day 28 |

End point description:

To demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in stratified adult participants with ventilated nosocomial pneumonia (VNP) based on the difference in all-cause mortality rates in the intent-to-treat (ITT) population using a non-inferiority margin of 12.5%. The estimated adjusted percentage was a weighted average across all strata, constructed using Mehrotra-Railkar continuity corrected minimum risk (MRc) stratum weights. The ITT population consisted of all randomized participants with documented informed consent, regardless of whether or not they received study drug.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day 28

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 362 | 364 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 97.5%) | 24.0 (18.31 to 28.09) | 25.3 (19.43 to 29.08) | | |

### Statistical analyses

| **Statistical analysis title** | Ceftolozane/Tazobactam vs Meropenem |
|---|---|

Statistical analysis description:

The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The 97.5% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference.

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |

| | |
|---|---|
| Number of subjects included in analysis | 726 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Difference in Percentage of Participants |
| Point estimate | 1.1 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -6.03 |
| upper limit | 8.28 |

## Secondary: Percentage of Participants with All Cause Mortality in the Microbiological Intent-to-Treat (mITT) Population - Day 28

| | |
|---|---|
| End point title | Percentage of Participants with All Cause Mortality in the Microbiological Intent-to-Treat (mITT) Population - Day 28 |

End point description:

To compare the all cause mortality rates of participants in the ceftolozane/tazobactam versus meropenem arms in microbiological intent-to-treat (mITT) population. The mITT population was a subset of the ITT population that included any participant who received any amount of study drug and had at least 1 bacterial respiratory pathogen isolated from the baseline LRT culture that was susceptible to at least 1 of the study drugs.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day 28

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 264 | 247 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 20.1 (15.12 to 24.50) | 25.5 (18.89 to 29.35) | | |

### Statistical analyses

| **Statistical analysis title** | Ceftolozane/Tazobactam vs Meropenem |
|---|---|

Statistical analysis description:

The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The 95% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference.

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |

| | |
|---|---|
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage of Participants |
| Point estimate | 4.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.83 |
| upper limit | 11.75 |

## Secondary: The Percentage of Participants with Clinical Response of Clinical Cure at the Test-of-Cure (TOC) Visit in the Clinically Evaluable (CE) Population

| | |
|---|---|
| End point title | The Percentage of Participants with Clinical Response of Clinical Cure at the Test-of-Cure (TOC) Visit in the Clinically Evaluable (CE) Population |

End point description:

Clinical response at the TOC visit was defined as cure (complete resolution with no new signs of ventilated nosocomial pneumonia [VNP]), failure (progression, relapse or recurrence of VNP) or indeterminate (no evaluable study data). A favorable clinical response is a clinical cure. A missing clinical response will be considered indeterminate unless the clinical outcome at the EOT visit was failure.The data-as-observed (DAO) approach was used where participants with missing clinical responses, including indeterminate outcomes, are excluded from the analysis population. The CE population was a subset of the ITT population that included any participant who received study drug, adhered to the study protocol through the TOC visit, and had an evaluable clinical outcome (either Cure or Failure) at the TOC visit (or were classified as a clinical failure prior to the TOC visit).

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

7 to 14 days after last dose of study drug (Up to ~Day 30)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 218 | 221 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 63.8 (57.50 to 70.11) | 64.7 (58.83 to 71.19) | | |

### Statistical analyses

| **Statistical analysis title** | Ceftolozane/Tazobactam vs. Meropenem |
|---|---|

Statistical analysis description:

The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The 95% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference.

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |

| | |
|---|---|
| Number of subjects included in analysis | 439 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage of Participants |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.21 |
| upper limit | 7.67 |

## Secondary: Percentage of Participants with Per-Participant Microbiological Response of Cure or Presumed Cure at the Test-of-Cure (TOC) Visit in the Microbiologically Evaluable (ME) Population

| | |
|---|---|
| End point title | Percentage of Participants with Per-Participant Microbiological Response of Cure or Presumed Cure at the Test-of-Cure (TOC) Visit in the Microbiologically Evaluable (ME) Population |

End point description:

The per-participant microbiological response will be determined based on the individual microbiological outcomes for each baseline pathogen. A microbiological response at the TOC visit was defined as cure (baseline pathogens eradicated), failure (baseline pathogen is persistent) or indeterminate (no evaluable respiratory material). A favorable microbiological response is a microbiological cure or presumed cure. The data-as-observed (DAO) approach was used where participants with missing clinical responses, including indeterminate outcomes, are excluded from the analysis population. The ME population was a subset of the mITT population that included any participants who adhered to the study protocol through the TOC visit, had an evaluable clinical outcome (Cure or Failure) at the TOC visit and had at least 1 bacterial respiratory pathogen (at the appropriate CFU/mL threshold) isolated from the baseline LRT culture.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

7 to 14 days after last dose of study drug (Up to ~Day 30)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 118 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 70.4 (61.37 to 77.55) | 62.7 (54.12 to 71.24) | | |

### Statistical analyses

| **Statistical analysis title** | Ceftolozane/Tazobactam vs. Meropenem |
|---|---|

Statistical analysis description:

The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The 95% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference.

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |

| | |
|---|---|
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage of Participants |
| Point estimate | 7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.11 |
| upper limit | 18.93 |

## Secondary: Percentage of Participants with Microbiological Response of Eradication or Presumed Eradication, by Pathogen, at the Test-of-Cure (TOC) Visit in the Microbiologically Evaluable (ME) Population (>=10 Isolates at Baseline)

| | |
|---|---|
| End point title | Percentage of Participants with Microbiological Response of Eradication or Presumed Eradication, by Pathogen, at the Test-of-Cure (TOC) Visit in the Microbiologically Evaluable (ME) Population (>=10 Isolates at Baseline) |

End point description:

The microbiological outcome was classified as "eradication", “presumed eradication”, "persistence”, ‘presumed persistence”, "indeterminate" or “recurrence.” "Eradication" was defined as a ≥1- log reduction in bacterial burden of the original baseline LRT pathogen AND a per pathogen count of ≤10^4 colony-forming unit (CFU)/mL for endotracheal aspirate (ETA) or sputum specimens, ≤10^3 CFU/mL for a bronchoalveolar lavage (BAL) specimen, or ≤10^2 CFU/mL for a protected brush specimen (PBS) from a follow-up LRT culture. Presumed eradication was defined as an absence of material to culture (e.g. inability to obtain a culture in an extubated patient) in a patient deemed a clinical cure. The number analyzed for each pathogen represents the number of participants in the ME population (those who adhered to protocol, had an evaluable clinical outcome, and at least 1 bacterial respiratory pathogen) with that specific pathogen.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

7 to 14 days after last dose of study drug (Up to ~Day 30)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 118 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Gram-Negative (n= 113, 117) | 69.9 (60.91 to 77.60) | 62.4 (53.35 to 70.64) | | |
| Pseudomonas aeruginosa (n= 29, 38) | 79.3 (61.61 to 90.15) | 55.3 (39.71 to 69.85) | | |
| Enterobacteriaceae (n= 83, 90) | 68.7 (58.06 to 77.64) | 65.6 (55.28 to 74.55) | | |
| Escherichia coli (n= 23, 23) | 78.3 (58.10 to 90.34) | 73.9 (53.53 to 87.45) | | |
| Klebsiella pneumonia (n= 42, 48) | 71.4 (56.43 to 82.83) | 66.7 (52.54 to 78.32) | | |
| Proteus mirabilis (n= 11, 10) | 63.6 (35.38 to 84.83) | 70.0 (39.68 to 89.22) | | |

| | | | | |
|---|---|---|---|---|
| Haemophilus influenza (n= 12, 8) | 91.7 (64.61 to 98.51) | 50.0 (21.52 to 78.48) | | |
| Enterobacter cloacae (n= 7, 8) | 57.1 (25.05 to 84.18) | 75.0 (40.93 to 92.85) | | |
| Klebsiella oxytoca (n= 8, 7) | 87.5 (52.91 to 97.76) | 57.1 (25.05 to 84.18) | | |
| Serratia marcescens (n= 5, 6) | 40.0 (11.76 to 76.93) | 50.0 (18.76 to 81.24) | | |
| Acinetobacter baumannii (n= 6, 5) | 33.3 (9.68 to 70.00) | 80.0 (37.55 to 96.38) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with All-Cause Mortality in the Intent-to-Treat (ITT) Population - Day 14

| | |
|---|---|
| End point title | Percentage of Participants with All-Cause Mortality in the Intent-to-Treat (ITT) Population - Day 14 |

End point description:

To compare the all cause mortality rates of participants (ceftolozane/tazobactam versus meropenem arms). Participants whose mortality outcomes are missing or unknown are analysed as deceased. The ITT population consisted of all randomized participants with documented informed consent, regardless of whether or not they received study drug.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day 14

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 362 | 364 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 14.1 (10.48 to 17.57) | 12.9 (9.31 to 15.86) | | |

### Statistical analyses

| **Statistical analysis title** | Ceftolozane/Tazobactam vs. Meropenem |
|---|---|

Statistical analysis description:

The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The 95% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference.

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |

| | |
|---|---|
| Number of subjects included in analysis | 726 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage of Participants |
| Point estimate | -1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.41 |
| upper limit | 3.57 |

## Secondary: Percentage of Participants with Clinical Response of Clinical Cure at the End-of-Therapy (EOT) Visit in the Intent-to-Treat (ITT) Population

| | |
|---|---|
| End point title | Percentage of Participants with Clinical Response of Clinical Cure at the End-of-Therapy (EOT) Visit in the Intent-to-Treat (ITT) Population |

End point description:

To compare the clinical response rates at the EOT visit for ceftolozane/tazobactam versus meropenem. Clinical response at the EOT visit was defined as cure (complete resolution with no new signs of VNP), failure (progression, relapse or recurrence of VNP) or indeterminate (no evaluable study data). A favorable clinical response is a clinical cure. A missing clinical response will be considered indeterminate. The ITT population consisted of all randomized participants with documented informed consent, regardless of whether or not they received study drug.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Within 24 hours after last dose of study drug (Up to ~Day 15)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 362 | 364 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 66.0 (61.38 to 71.03) | 66.8 (62.31 to 71.77) | | |

### Statistical analyses

| **Statistical analysis title** | Ceftolozane/Tazobactam vs. Meropenem |
|---|---|

Statistical analysis description:

The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The 95% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference.

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |

| | |
|---|---|
| Number of subjects included in analysis | 726 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage of Participants |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.67 |
| upper limit | 6.04 |

## Secondary: Percentage of Participants with Per-Participant Microbiological Response of Cure or Presumed Cure at the End-of-Therapy (EOT) Visit in the Microbiologically Evaluable (ME) Population

| | |
|---|---|
| End point title | Percentage of Participants with Per-Participant Microbiological Response of Cure or Presumed Cure at the End-of-Therapy (EOT) Visit in the Microbiologically Evaluable (ME) Population |

End point description:

The per-participant microbiological response will be determined based on the individual microbiological outcomes for each baseline pathogen. A microbiological response at the EOT visit was defined as cure (baseline pathogens eradicated), failure (baseline pathogen is persistent) or indeterminate (no evaluable respiratory material). A favorable microbiological response is a microbiological cure or presumed cure. The data-as-observed (DAO) approach was used where participants with missing clinical responses, including indeterminate outcomes, are excluded from the analysis population. The ME population was a subset of the mITT population that included any participants who adhered to the study protocol through the TOC visit, had an evaluable clinical outcome (Cure or Failure) at the TOC visit and had at least 1 bacterial respiratory pathogen (at the appropriate CFU/mL threshold) isolated from the baseline LRT culture.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Within 24 hours after last dose of study drug (Up to ~Day 15)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 118 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 80.9 (71.51 to 86.33) | 78.8 (70.25 to 84.90) | | |

### Statistical analyses

| **Statistical analysis title** | Ceftolozane/Tazobactam vs. Meropenem |
|---|---|

Statistical analysis description:

The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The 95% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference.

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |

| | |
|---|---|
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage of Participants |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.91 |
| upper limit | 12.02 |

## Secondary: Percentage of Participants with Clinical Response of Clinical Cure at the Late Follow-up (LFU) Visit in the Clinically Evaluable (CE) Population

| | |
|---|---|
| End point title | Percentage of Participants with Clinical Response of Clinical Cure at the Late Follow-up (LFU) Visit in the Clinically Evaluable (CE) Population |

End point description:

To compare the clinical response rates at the Late Follow-up (LFU) visit for ceftolozane/tazobactam versus meropenem in the CE population. Clinical response at the LFU visit will be classified as sustained cure, relapse, or indeterminate only in participants deemed a clinical cure at the TOC visit. A favorable clinical response is "sustained clinical cure." The CE population was a subset of the ITT population that included any participant who received study drug, adhered to the study protocol through the TOC visit, and had an evaluable clinical outcome (either Cure or Failure) at the TOC visit (or were classified as a clinical failureprior to the TOC visit).

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Up to 35 days after last dose of study drug (Up to ~Day 50)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 218 | 221 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 52.8 | 51.6 | | |

### Statistical analyses

| **Statistical analysis title** | Ceftolozane/Tazobactam vs. Meropenem |
|---|---|

Statistical analysis description:

The percent difference between groups is the weighted proportion difference using Mehrotra-Railkar continuity-corrected-minimum risk (MRc) stratum weights for strata of diagnosis (VABP, ventilated HABP) and age (<65, >= 65) categories. The 95% CI was stratified Wilson intervals for group percentages and a stratified Newcombe interval for the difference.

| | |
|---|---|
| Comparison groups | Ceftolozane/Tazobactam v Meropenem |

| | |
|---|---|
| Number of subjects included in analysis | 439 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage of Participants |
| Point estimate | 3.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.38 |
| upper limit | 10.44 |

## Secondary: Percentage of Participants Who Report 1 or More Adverse Event (AE)

| | |
|---|---|
| End point title | Percentage of Participants Who Report 1 or More Adverse Event (AE) |

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. All safety analyses were based on a subset of the ITT population (the Safety Population), which included randomized participants who received any amount (i.e., full or partial dose) of study drug. All participants received their randomly assigned treatments, and no participants with important deviations were excluded from the safety population.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Up to 35 days after last dose of study drug (Up to ~Day 50)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 361 | 359 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 85.9 | 83.3 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Any Serious Adverse Event (SAE)

| | |
|---|---|
| End point title | Percentage of Participants with Any Serious Adverse Event (SAE) |

End point description:

A serious adverse event (SAE) is an AE that results in death, is life threatening, requires or prolongs an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is another important medical event deemed such by medical or scientific judgment. All safety analyses were based on a subset of the ITT population (the Safety Population), which included randomized participants who received any amount (i.e., full or partial dose) of study drug. All participants received their randomly assigned treatments, and no participants with important

deviations were excluded from the safety population.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 35 days after last dose of study drug (Up to ~Day 50)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 361 | 359 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 42.1 | 35.9 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Discontinuing Study Drug Due to an AE

| End point title | Percentage of Participants Discontinuing Study Drug Due to an AE |
|---|---|

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. All participants received their randomly assigned treatments, and no participants with important deviations were excluded from the safety population.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 14 days after the first dose of study drug (Up to ~Day 15)

| **End point values** | Ceftolozane/Tazobactam | Meropenem | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 361 | 359 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 10.2 | 11.7 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 35 days after last dose of study drug (Up to ~Day 50)

Adverse event reporting additional description:

All safety analyses were based on a subset of the ITT population (the Safety Population) who received any amount of study drug. All participants received their randomly assigned treatments, and no participants with important deviations were excluded from the safety population. Discontinuations due to adverse events (AEs) include deaths.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Ceftolozane/tazobactam |

Reporting group description:

Participants receive 3000 mg ceftolozane/tazobactam (comprising 2000 mg ceftolozane and 1000 mg tazobactam) administered as an IV infusion every 8 hours (q8h).

| | |
|---|---|
| Reporting group title | Meropenem |

Reporting group description:

Participants receive 1000 mg meropenem administered as an IV infusion every 8 hours (q8h).

| Serious adverse events | Ceftolozane/tazobactam | Meropenem | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 152 / 361 (42.11%) | 129 / 359 (35.93%) | |
| number of deaths (all causes) | 105 | 101 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant peritoneal neoplasm | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal cancer | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Arterial thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemodynamic instability | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 2 / 361 (0.55%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Neurogenic shock | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| General disorders and administration site conditions | | | |
| Brain death | | | |
| subjects affected / exposed | 3 / 361 (0.83%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Cardiac death | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Death | | | |
| subjects affected / exposed | 3 / 361 (0.83%) | 4 / 359 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 4 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 14 / 361 (3.88%) | 9 / 359 (2.51%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 14 | 0 / 9 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Acquired tracheo-oesophageal fistula | | | |
| subjects affected / exposed | 3 / 361 (0.83%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute lung injury | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 361 (0.55%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 5 / 359 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chronic respiratory failure | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mediastinal effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organising pneumonia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumomediastinum | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 3 / 361 (0.83%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 4 / 361 (1.11%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 6 / 361 (1.66%) | 5 / 359 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 4 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory distress | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 361 (0.28%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 10 / 361 (2.77%) | 6 / 359 (1.67%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 4 | |
| Tracheal stenosis | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Abdominal wound dehiscence | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder injury | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain herniation | | | |
| subjects affected / exposed | 3 / 361 (0.83%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal anastomotic leak | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheal haemorrhage | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheal injury | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Cerebral arteriovenous malformation haemorrhagic | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 361 (0.55%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Bradycardia | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 8 / 361 (2.22%) | 6 / 359 (1.67%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 2 | |
| Cardiac failure | | | |
| subjects affected / exposed | 7 / 361 (1.94%) | 3 / 359 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 3 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 9 / 361 (2.49%) | 7 / 359 (1.95%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 9 | 0 / 6 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 4 / 361 (1.11%) | 4 / 359 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiovascular insufficiency | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 361 (0.55%) | 4 / 359 (1.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulseless electrical activity | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 2 / 361 (0.55%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Amyotrophic lateral sclerosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Apallic syndrome | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Brain injury | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Brain midline shift | | | |
| subjects affected / exposed | 4 / 361 (1.11%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | |
| Brain oedema | | | |
| subjects affected / exposed | 8 / 361 (2.22%) | 8 / 359 (2.23%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 8 | |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 5 / 361 (1.39%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 0 | |
| Cerebral infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral vasoconstriction | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 3 / 361 (0.83%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Hydrocephalus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 361 (0.00%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraventricular haemorrhage | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Neurological decompensation | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord oedema | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Wernicke's encephalopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Gastroduodenal haemorrhage | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 4 / 361 (1.11%) | 3 / 359 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Gastrointestinal ischaemia | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic erosive gastritis | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hernial eventration | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peptic ulcer | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Hepatobiliary disorders | | | |
| Hepatitis cholestatic | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 361 (0.55%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 9 / 361 (2.49%) | 3 / 359 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal infection | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess neck | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| CNS ventriculitis | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 361 (0.83%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis bacterial | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endotoxaemia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Enterobacter bacteraemia | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 3 / 359 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 3 / 359 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 361 (0.83%) | 3 / 359 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 5 / 361 (1.39%) | 3 / 359 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 2 | |
| Septic encephalopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 13 / 361 (3.60%) | 14 / 359 (3.90%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 14 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 9 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 361 (0.28%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 2 / 359 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 361 (0.00%) | 1 / 359 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 2 / 361 (0.55%) | 0 / 359 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Ceftolozane/tazobactam | Meropenem | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 113 / 361 (31.30%) | 111 / 359 (30.92%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 20 / 361 (5.54%) | 14 / 359 (3.90%) | |
| occurrences (all) | 21 | 14 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 32 / 361 (8.86%) | 38 / 359 (10.58%) | |
| occurrences (all) | 32 | 45 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 23 / 361 (6.37%) | 25 / 359 (6.96%) | |
| occurrences (all) | 23 | 28 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hydrothorax | | | |
| subjects affected / exposed | 16 / 361 (4.43%) | 20 / 359 (5.57%) | |
| occurrences (all) | 17 | 24 | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 25 / 361 (6.93%) | 17 / 359 (4.74%) | |
| occurrences (all) | 30 | 22 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 23 / 361 (6.37%) | 25 / 359 (6.96%) | |
| occurrences (all) | 24 | 27 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 February 2013 | Amendment 1: (version 2.0) Secondary and exploratory endpoints were updated. |
| 27 November 2013 | Amendment 2: (Version 3.0) Updated protocol title and the benefits and risk summary to include new information for the new comparator, meropenem. |
| 14 March 2014 | Amendment 3: (Version 4.0) Updated protocol with new clinical information on ceftolozane/tazobactam, the results from the Phase 3 complicated urinary tract infection (cUTI) and complicated intra abdominal infection (cIAI) trials |
| 22 October 2014 | Amendment 4: (Version 5.0) A key secondary endpoint was added and proportion of subjects with ventilator-associated bacterial pneumonia (VABP) was increased. |
| 15 March 2016 | Amendment 5: (Version 6.0) Updated standard of care to a treatment duration of 8-14 days and also updated inclusion and exclusion criteria. |
| 25 August 2017 | Amendment 8: (Version 7.0) Changed primary objective to clinical response at time of cure (TOC) in the intent to treat (ITT) analysis set and changed another primary objective to secondary objective to prioritize analyses of key efficacy measures. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported