



## 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
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##### 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:

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### 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
<b>Arm title</b>	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.

<b>Arm title</b>	Meropenem
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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.

<b>Number of subjects in period 1</b>	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 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 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 HAP) 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
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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
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End point timeframe:

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

<b>End point values</b>	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**

<b>Statistical analysis title</b>	Ceftolozane/Tazobactam vs. Meropenem
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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
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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
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#### 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
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#### 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
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#### 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
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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 ( $\geq 10$  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 ( $\geq 10$ Isolates at Baseline)
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End point description:

The microbiological outcome was classified as "eradication", "presumed eradication", "persistence", "presumed persistence", "indeterminate" or "recurrence." "Eradication" was defined as a  $\geq 1$ - log reduction in bacterial burden of the original baseline LRT pathogen AND a per pathogen count of  $\leq 10^4$  colony-forming unit (CFU)/mL for endotracheal aspirate (ETA) or sputum specimens,  $\leq 10^3$  CFU/mL for a bronchoalveolar lavage (BAL) specimen, or  $\leq 10^2$  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
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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
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#### 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
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#### 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
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#### 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
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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
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#### 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 failure prior to the TOC visit).

End point type	Secondary
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#### 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
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#### 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
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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)
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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
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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)
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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/Ta zobactam	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
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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/Ta zobactam	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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	Ceftolozane/tazobactam
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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
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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	
<b>Blood and lymphatic system disorders</b>			
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	
<b>Ear and labyrinth disorders</b>			
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	
<b>Gastrointestinal disorders</b>			
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 %

<b>Non-serious adverse events</b>	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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported