Clinical trial results:
Phase III, Randomized, Multicentre, Double-blind, Double-dummy, Parallel-group Comparative Study to Determine the Efficacy, Safety And Tolerability of Ceftazidime-Avibactam (CAZ-AVI) Versus Meropenem in the Treatment of Nosocomial Pneumonia (NP) Including Ventilator-Associated Pneumonia (VAP) in Hospitalised Adults

Summary

EudraCT number	2012-004006-96
Trial protocol	CZ HU GB ES IT PL BG LV SI LT GR RO
Global end of trial date	07 January 2016

Results information

Result version number	v1 (current)
This version publication date	06 January 2017
First version publication date	06 January 2017

Trial information

Trial identification

Sponsor protocol code	D4281C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01808092
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	AstraZeneca AB, 151 85 Södertälje, Sweden,
Public contact	MSD: Joseph Chow, AstraZeneca, Joseph.Chow@astrazeneca.com
Scientific contact	David Wilson, Statistical Team Leader - Infection, AstraZeneca, +44 1625 517830 x, David.wilson2@astrazeneca.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	25 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 January 2016
Global end of trial reached?	Yes
Global end of trial date	07 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the non-inferiority of ceftazidime-avibactam (CAZ-AVI) compared to meropenem with respect to clinical cure at the test of cure (TOC) visit (Day 21 - 25 from randomization) in patients in the clinically modified intent-to-treat (cMITT) population and patients in the clinically evaluable (CE) population.

Protection of trial subjects:

The final study protocol, including the final version of the informed consent form and any other written information or materials provided to the patients was approved by an independent ethics committee (EC) and/or institutional review board (IRB). The investigator ensured the distribution of these documents to the applicable EC and to the study center personnel. This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1) Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 April 2013
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	Brazil: 85
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	China: 274
Country: Number of subjects enrolled	Czech Republic: 95
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	India: 78
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Peru: 3
Country: Number of subjects enrolled	Philippines: 28
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Romania: 5

Country: Number of subjects enrolled	Russian Federation: 24
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Ukraine: 27
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Vietnam: 20
Worldwide total number of subjects	808
EEA total number of subjects	218

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)	394
From 65 to 84 years	376
85 years and over	38

Subject disposition

Recruitment

Recruitment details:

Overall, 879 patients were randomized, from 4 geographic regions. The first patient was enrolled on 13 Apr. 2013 and the last patient last visit was on 07 Jan. 2016. Summary tables exclude 62 patients with moderate/severe renal impairment recruited prior to a protocol amendment to the dose regimen for such patients. 817 randomized and 808 treated.

Pre-assignment

Screening details:

After obtaining written informed consent patients underwent a preliminary evaluation for eligibility within the 24-hour period prior to initiation of IV study therapy. Eligible patients were randomized to 1 of 2 treatments in a 1:1 ratio according to the randomization schedule.

Period 1

Period 1 title	Prior to Study Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	CAZ-AVI

Arm description:

2000mg ceftazidime / 500mg avibactam intravenous (IV) infused over 2 hours plus appropriate placebo to meropenem

Arm type	Experimental
Investigational medicinal product name	Ceftazidime-Avibactam
Investigational medicinal product code	CAZ-AVI
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- 2000mg ceftazidime / 500mg avibactam Intra-Venous (IV) infused over 2 hours plus appropriate placebo to meropenem

Arm title	Meropenem

Arm description:

meropenem 1000mg IV infused over 30 minutes plus CAZ-AVI placebo

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

Dosage and administration details:

- meropenem 1000mg IV infused over 30 minutes plus CAZ-AVI placebo

Number of subjects in period 1	CAZ-AVI	Meropenem
Started	405	403
Completed	355	363
Not completed	50	40
Adverse event, serious fatal	37	28
Consent withdrawn by subject	8	4
Other Eligibility criteria	2	1
Lost to follow-up	3	7

Baseline characteristics

Reporting groups	
Reporting group title	CAZ-AVI
Reporting group description:	
2000mg ceftazidime / 500mg avibactam intravenous (IV) infused over 2 hours plus appropriate placebo to meropenem	
Reporting group title	Meropenem
Reporting group description:	
meropenem 1000mg IV infused over 30 minutes plus CAZ-AVI placebo	

Reporting group values	CAZ-AVI	Meropenem	Total
Number of subjects	405	403	808
Age categorical			
This is based on safety analysis set			
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 (18-45 years)	74	74	148
From 46-64 years	124	122	246
From 65-74 years	97	95	192
From 75-90 years	110	112	222
Age Continuous | Units: Years			
arithmetic mean	61.8	61.7	
standard deviation	± 16.76	± 17.57	-
Gender, Male/Female Units: Participants			
Female	101	105	206
Male	304	298	602

End points

End points reporting groups

Reporting group title	CAZ-AVI
Reporting group description:	
2000mg ceftazidime / 500mg avibactam intravenous (IV) infused over 2 hours plus appropriate placebo to meropenem	
Reporting group title	Meropenem
Reporting group description:	
meropenem 1000mg IV infused over 30 minutes plus CAZ-AVI placebo	

Primary: The proportion of patients with clinical cure at test-of-cure (TOC) visit in the clinically modified intent-to-treat analysis set (co-primary analyses)

End point title	The proportion of patients with clinical cure at test-of-cure (TOC) visit in the clinically modified intent-to-treat analysis set (co-primary analyses)
End point description:	
The proportion of patients meeting the cure criteria: the patient was not a clinical failure at end of treatment and the patient is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for Nosocomial Pneumonia was taken between end of treatment and test-of-cure inclusive.	
End point type	Primary
End point timeframe:	
At the test-of-cure (TOC) visit (Day 21 to 25)	

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	370		
Units: participants				
Clinical cure	245	270		
Clinical failure	79	70		
Indeterminate	32	30		

Statistical analyses

Statistical analysis title	Proportion of patients with clinical cure
Statistical analysis description:	
Statistical analysis for the proportion of patients with clinical cure at TOC in cMITT analysis set	
Comparison groups	CAZ-AVI v Meropenem

Number of subjects included in analysis	726
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.007 [1]
Method	% Risk Difference (RD)
Parameter estimate	percentage: units for RD are %
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.76
upper limit	2.46

Notes:

[1] - P-value for 1-sided test at test of cure (TOC) with a -12.5% non-inferiority margin, i.e. H0: diff <= -12.5%.

Primary: The proportion of patients with clinical cure at test-of-cure (TOC) visit in the clinically evaluable at TOC analysis set (co-primary analyses)

End point title	The proportion of patients with clinical cure at test-of-cure (TOC) visit in the clinically evaluable at TOC analysis set (co-primary analyses)

End point description:

The proportion of patients meeting the cure criteria: the patient was not a clinical failure at end of treatment and the patient is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for Nosocomial Pneumonia was taken between end of treatment and test-of-cure inclusive.

End point type	Primary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	270		
Units: participants				
Clinical cure	199	211		
Clinical failure	58	59		

Statistical analyses

Statistical analysis title	Proportion of patients with clinical cure

Statistical analysis description:

Statistical analysis for the proportion of patients with clinical cure at TOC in CE at TOC analysis set

Comparison groups	CAZ-AVI v Meropenem

Number of subjects included in analysis	527
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [2]
Method	% Risk Difference (RD)
Parameter estimate	percentage: units for RD are %
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.86
upper limit	6.39

Notes:

[2] - P-value for 1-sided test at test of cure (TOC) with a -12.5% non-inferiority margin, i.e. H0: diff <= -12.5%.

Secondary: The proportion of patients with clinical cure at test-of-cure (TOC) visit in the microbiologically modified intent-to-treat analysis set

End point title	The proportion of patients with clinical cure at test-of-cure (TOC) visit in the microbiologically modified intent-to-treat analysis set

End point description:

The proportion of patients meeting the cure criteria: the patient was not a clinical failure at end of treatment and the patient is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for Nosocomial Pneumonia was taken between end of treatment and test-of-cure inclusive.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
Clinical cure	120	138		
Clinical failure	37	34		
Indeterminate	14	12		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure at test-of-cure (TOC) visit in the extended microbiologically evaluable analysis set

End point title	The proportion of patients with clinical cure at test-of-cure (TOC) visit in the extended microbiologically evaluable analysis set

End point description:

The proportion of patients meeting the cure criteria: the patient was not a clinical failure at end of

treatment and the patient is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for Nosocomial Pneumonia was taken between end of treatment and test-of-cure inclusive.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: participants				
Clinical cure	96	103		
Clinical failure	29	28		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure at test-of-cure (TOC) visit in the microbiologically evaluable analysis set

End point title	The proportion of patients with clinical cure at test-of-cure (TOC) visit in the microbiologically evaluable analysis set

End point description:

The proportion of patients meeting the cure criteria: the patient was not a clinical failure at end of treatment and the patient is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for Nosocomial Pneumonia was taken between end of treatment and test-of-cure inclusive.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	118		
Units: participants				
Clinical cure	85	94		
Clinical failure	22	24		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set

End point title	The proportion of patients with clinical cure at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set

End point description:

The proportion of patients meeting the cure criteria: the patient is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for Nosocomial Pneumonia are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for Nosocomial Pneumonia prior to end of treatment.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
Clinical cure	143	161		
Clinical failure	23	18		
Indeterminate	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure at end of treatment (EOT) visit in clinically modified intent-to-treat analysis set

End point title	The proportion of patients with clinical cure at end of treatment (EOT) visit in clinically modified intent-to-treat analysis set

End point description:

The proportion of patients meeting the cure criteria: the patient is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for Nosocomial Pneumonia are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for Nosocomial Pneumonia prior to end of treatment.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	370		
Units: participants				
Clinical cure	292	309		
Clinical failure	50	45		

Indeterminate	14	16		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure at end of treatment (EOT) visit in clinically evaluable analysis set

End point title	The proportion of patients with clinical cure at end of treatment (EOT) visit in clinically evaluable analysis set

End point description:

The proportion of patients meeting the cure criteria: the patient is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for Nosocomial Pneumonia are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for Nosocomial Pneumonia prior to end of treatment.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	306		
Units: participants				
Clinical cure	253	268		
Clinical failure	38	38		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure at end of treatment (EOT) visit in extended microbiologically evaluable analysis set

End point title	The proportion of patients with clinical cure at end of treatment (EOT) visit in extended microbiologically evaluable analysis set

End point description:

The proportion of patients meeting the cure criteria: the patient is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for Nosocomial Pneumonia are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for Nosocomial Pneumonia prior to end of treatment.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	151		
Units: participants				
Clinical cure	125	135		
Clinical failure	18	16		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure at end of treatment (EOT) visit in microbiologically evaluable analysis set

End point title	The proportion of patients with clinical cure at end of treatment (EOT) visit in microbiologically evaluable analysis set

End point description:

The proportion of patients meeting the cure criteria: the patient is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for Nosocomial Pneumonia are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for Nosocomial Pneumonia prior to end of treatment.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	138		
Units: participants				
Clinical cure	110	126		
Clinical failure	12	12		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with a favorable per-patient microbiologic response at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set

End point title	The proportion of patients with a favorable per-patient microbiologic response at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
Favorable	128	148		
Unfavorable	38	31		
Indeterminate	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with a favorable per-patient microbiologic response at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set

End point title	The proportion of patients with a favorable per-patient microbiologic response at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
Favorable	95	118		
Unfavorable	64	54		
Indeterminate	12	12		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with a favorable per-patient microbiologic response at end of treatment (EOT) visit in extended microbiologically evaluable at end of treatment analysis set

End point title	The proportion of patients with a favorable per-patient microbiologic response at end of treatment (EOT) visit in extended microbiologically evaluable at end of treatment analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	151		
Units: participants				
Favorable	112	123		
Unfavorable	31	28		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with a favorable per-patient microbiologic response at test-of-cure (TOC) visit in extended microbiologically evaluable at test-of-cure analysis set

End point title	The proportion of patients with a favorable per-patient microbiologic response at test-of-cure (TOC) visit in extended microbiologically evaluable at test-of-cure analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: participants				
Favorable	80	89		
Unfavorable	45	42		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with a favorable per-patient microbiologic response at end of treatment (EOT) visit in microbiologically evaluable at end of treatment analysis set

End point title	The proportion of patients with a favorable per-patient microbiologic response at end of treatment (EOT) visit in microbiologically evaluable at end of treatment analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	138		
Units: participants				
Favorable	96	112		
Unfavorable	26	26		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with a favorable per-patient microbiologic response at test-of-cure (TOC) visit in microbiologically evaluable at test-of-cure

analysis set

End point title	The proportion of patients with a favorable per-patient microbiologic response at test-of-cure (TOC) visit in microbiologically evaluable at test-of-cure analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	118		
Units: participants				
Favorable	70	83		
Unfavorable	37	35		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set at end of treatment visit (pathogens in ≥10 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set at end of treatment visit (pathogens in ≥10 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants with favorable responses				
Enterobacter aerogenes (n=8, 8)	6	5		

Enterobacter cloacae (n=26, 22)	25	20		
Escherichia coli (n=17, 20)	15	18		
Klebsiella pneumoniae (n=59, 71)	49	65		
Proteus mirabilis (n=14, 12)	12	10		
Serratia marcescens (n=15, 13)	12	11		
Haemophilus influenzae (n=16, 25)	15	25		
Pseudomonas aeruginosa (n=58, 47)	33	27		
Staphylococcus aureus (n=24, 34)	21	32		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses at end of treatment (EOT) visit in extended microbiologically evaluable at end of treatment analysis set (pathogens in ≥10 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses at end of treatment (EOT) visit in extended microbiologically evaluable at end of treatment analysis set (pathogens in ≥10 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	151		
Units: participants with favorable responses				
Enterobacter aerogenes (n=6, 7)	4	5		
Enterobacter cloacae (n=22, 17)	22	17		
Escherichia coli (n=14, 18)	13	17		
Klebsiella pneumoniae (n=46, 57)	39	53		
Proteus mirabilis (n=9, 8)	8	6		
Serratia marcescens (n=13, 10)	12	8		
Haemophilus influenzae (n=14, 16)	14	16		
Pseudomonas aeruginosa (n=50, 41)	30	24		
Staphylococcus aureus (n=18, 26)	16	25		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses at end of treatment (EOT) visit in microbiologically evaluable at end of treatment analysis set (pathogens in ≥10 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses at end of treatment (EOT) visit in microbiologically evaluable at end of treatment analysis set (pathogens in ≥10 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	138		
Units: participants with favorable responses				
Enterobacter aerogenes (n=6, 7)	4	5		
Enterobacter cloacae (n=22, 17)	22	17		
Escherichia coli (n=13, 18)	13	17		
Klebsiella pneumoniae (n=45, 55)	38	51		
Proteus mirabilis (n=9, 8)	8	6		
Serratia marcescens (n=13, 10)	12	8		
Haemophilus influenzae (n=12, 15)	12	15		
Pseudomonas aeruginosa (n=38, 34)	22	19		
Staphylococcus aureus (n=16, 23)	14	22		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set at test-of-cure visit (pathogens in ≥10 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set at test-of-cure visit (pathogens in ≥10 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants with favorable responses				
Enterobacter aerogenes (n=8, 8)	5	5		
Enterobacter cloacae (n=26, 22)	21	13		
Escherichia coli (n=17, 20)	13	16		
Klebsiella pneumoniae (n=59, 71)	37	53		
Proteus mirabilis (n=14, 12)	11	8		
Serratia marcescens (n=15, 13)	10	8		
Haemophilus influenzae (n=16, 25)	14	23		
Pseudomonas aeruginosa (n=58, 47)	22	18		
Staphylococcus aureus (n=24, 34)	11	25		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses at test-of-cure (TOC) visit in extended microbiologically evaluable at test-of-cure analysis set (pathogens in ≥10 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses at test-of-cure (TOC) visit in extended microbiologically evaluable at test-of-cure analysis set (pathogens in ≥10 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	131		
Units: participants with favorable responses				
Enterobacter aerogenes (n=6, 5)	5	3		
Enterobacter cloacae (n=21, 11)	18	7		
Escherichia coli (n=11, 18)	10	16		

Klebsiella pneumoniae (n=37, 49)	29	39		
Proteus mirabilis (n=11, 8)	9	6		
Serratia marcescens (n=12, 8)	9	5		
Haemophilus influenzae (n=11, 13)	11	12		
Pseudomonas aeruginosa (n=42, 35)	18	14		
Staphylococcus aureus (n=14, 22)	5	17		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses at test-of-cure (TOC) visit in microbiologically evaluable at test-of-cure analysis set (pathogens in ≥10 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses at test-of-cure (TOC) visit in microbiologically evaluable at test-of-cure analysis set (pathogens in ≥10 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	118		
Units: participants with favorable responses				
Enterobacter aerogenes (n=6, 5)	5	3		
Enterobacter cloacae (n=21, 11)	18	7		
Escherichia coli (n=10, 18)	10	16		
Klebsiella pneumoniae (n=37, 47)	29	38		
Proteus mirabilis (n=11, 8)	9	6		
Serratia marcescens (n=12, 8)	9	5		
Haemophilus influenzae (n=9, 12)	9	11		
Pseudomonas aeruginosa (n=31, 28)	13	12		
Staphylococcus aureus (n=13, 19)	4	15		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in clinically modified intent-to-treat analysis set at end of treatment visit (pathogens in ≥5 patients)

End point title	The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in clinically modified intent-to-treat analysis set at end of treatment visit (pathogens in ≥5 patients)

End point description:

The proportion of patients meeting the cure criteria: the patient is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for Nosocomial Pneumonia are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for Nosocomial Pneumonia prior to end of treatment.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
All (n=45, 54)	40	45		
Enterobacteriaceae (n=34, 41)	32	33		
Enterobacter aerogenes (n=4, 2)	3	2		
Enterobacter cloacae (n=6, 6)	6	4		
Escherichia coli (n=6, 5)	5	3		
Klebsiella pneumoniae (n=20, 30)	20	26		
Gram- pathogens not Enterobacteriaceae (n=11,16)	8	14		
Pseudomonas aeruginosa (n=11, 15)	8	13		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in clinically evaluable at end of treatment analysis set (pathogens in ≥5 patients)

End point title	The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in clinically evaluable at end of treatment analysis set (pathogens in ≥5 patients)

End point description:

The proportion of patients meeting the cure criteria: the patient is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for Nosocomial Pneumonia are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for Nosocomial Pneumonia prior to end of treatment.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	306		
Units: participants				
All (n=39, 49)	35	42		
Enterobacteriaceae (n=29, 37)	27	31		
Enterobacter aerogenes (n=4, 2)	3	2		
Enterobacter cloacae (n=6, 5)	6	3		
Escherichia coli (n=6, 4)	5	3		
Klebsiella pneumoniae (n=16, 28)	16	25		
Gram- pathogens not Enterobacteriaceae (n=10,14)	8	13		
Pseudomonas aeruginosa (n=10, 13)	8	12		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically evaluable at end of treatment analysis set (pathogens in ≥5 patients)

End point title	The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically evaluable at end of treatment analysis set (pathogens in ≥5 patients)

End point description:

The proportion of patients meeting the cure criteria: the patient is alive and all signs and symptoms of pneumonia have resolved or improved such that all antibacterial therapies for Nosocomial Pneumonia are stopped. No antibacterial therapy other than those outlined by the protocol has been administered for Nosocomial Pneumonia prior to end of treatment.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	138		
Units: participants				
All (n=32, 40)	31	36		
Enterobacteriaceae (n=28, 35)	27	31		
Enterobacter aerogenes (n=4, 2)	3	2		
Enterobacter cloacae (n=6, 5)	6	3		
Escherichia coli (n=5, 4)	5	3		
Klebsiella pneumoniae (n=16, 26)	16	25		

Gram- pathogens not Enterobacteriaceae (n=4,7)	4	7		
Pseudomonas aeruginosa (n=4, 6)	4	6		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in clinically modified intent-to-treat analysis set at test-of-cure visit (pathogens in ≥5 patients)

End point title	The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in clinically modified intent-to-treat analysis set at test-of-cure visit (pathogens in ≥5 patients)

End point description:

The proportion of patients meeting the cure criteria: the patient was not a clinical failure at end of treatment and the patient is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for Nosocomial Pneumonia was taken between end of treatment and test-of-cure inclusive.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
All (n=45, 54)	35	40		
Enterobacteriaceae (n=34, 41)	28	29		
Enterobacter aerogenes (n=4, 2)	3	2		
Enterobacter cloacae (n=6, 6)	6	4		
Escherichia coli (n=6, 5)	4	3		
Klebsiella pneumoniae (n=20, 30)	16	22		
Gram- pathogens not Enterobacteriaceae (n=11,16)	7	13		
Pseudomonas aeruginosa (n=11, 15)	7	13		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in clinically evaluable at test-of-cure analysis set (pathogens in ≥5 patients)

End point title	The proportion of patients with clinical cure in patients with

	pathogens resistant to ceftazidime at test-of-cure (TOC) visit in clinically evaluable at test-of-cure analysis set (pathogens in ≥5 patients)

End point description:

The proportion of patients meeting the cure criteria: the patient was not a clinical failure at end of treatment and the patient is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for Nosocomial Pneumonia was taken between end of treatment and test-of-cure inclusive.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	270		
Units: participants				
All (n=36, 41)	29	32		
Enterobacteriaceae (n=27, 30)	23	22		
Enterobacter cloacae (n=5, 5)	5	3		
Escherichia coli (n=5, 4)	4	3		
Klebsiella pneumoniae (n=14, 22)	12	17		
Gram- pathogens not Enterobacteriaceae (n=9,13)	6	12		
Pseudomonas aeruginosa (n=9, 13)	6	12		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically evaluable at test-of-cure analysis set (pathogens in ≥5 patients)

End point title	The proportion of patients with clinical cure in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically evaluable at test-of-cure analysis set (pathogens in ≥5 patients)

End point description:

The proportion of patients meeting the cure criteria: the patient was not a clinical failure at end of treatment and the patient is alive and all signs and symptoms of pneumonia have resolved or improved to an extent that no antibacterial therapy for Nosocomial Pneumonia was taken between end of treatment and test-of-cure inclusive.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	118		
Units: participants				
All (n=29, 32)	25	26		
Enterobacteriaceae (n=26, 28)	23	22		
Enterobacter cloacae (n=5, 5)	5	3		
Escherichia coli (n=4, 4)	4	3		
Klebsiella pneumoniae (n=14, 20)	12	17		
Gram- pathogens not Enterobacteriaceae (n=3,6)	2	6		
Pseudomonas aeruginosa (n=3, 6)	2	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set at end of treatment visit

End point title	Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set at end of treatment visit

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	54		
Units: participants				
Favorable	35	39		
Unfavorable	10	13		
Indeterminate	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in extended microbiologically evaluable at end of treatment analysis set

End point title	Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in extended microbiologically evaluable at end of treatment analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	49		
Units: participants				
Favorable	31	36		
Unfavorable	9	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically evaluable at end of treatment analysis set

End point title	Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically evaluable at end of treatment analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	40		
Units: participants				
Favorable	26	29		
Unfavorable	7	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set at test-of-cure visit

End point title	Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set at test-of-cure visit

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	54		
Units: participants				
Favorable	27	27		
Unfavorable	16	23		
Indeterminate	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in extended microbiologically evaluable at test-of-cure analysis set

End point title	Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in extended microbiologically evaluable at test-of-cure analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	41		
Units: participants				
Favorable	23	21		
Unfavorable	14	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically evaluable at test-of-cure analysis set

End point title	Proportion of patients with a favorable per-patient microbiologic response in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically evaluable at test-of-cure analysis set

End point description:

Per-patient "favorable" response indicates that all of the patient's baseline pathogens are "eradicated" or "presumed eradicated". Eradication is defined as: source specimen demonstrates absence of the original baseline pathogen. Presumed eradication is defined as: source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: participants				
Favorable	21	18		
Unfavorable	9	14		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set at EOT visit (pathogens in ≥5 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically modified intent-to-treat analysis set at EOT visit (pathogens in ≥5 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	54		
Units: participants with favorable responses				
Enterobacter aerogenes (n=4, 2)	3	2		
Enterobacter cloacae (n=6, 6)	6	6		
Escherichia coli (n=6, 5)	5	4		
Klebsiella pneumoniae (n=20, 30)	18	26		
Pseudomonas aeruginosa (n=11, 15)	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in extended microbiologically evaluable at EOT analysis set (pathogens in ≥5 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in extended microbiologically evaluable at EOT analysis set (pathogens in ≥5 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	49		
Units: participants with favorable responses				
Enterobacter aerogenes (n=4, 2)	3	2		
Enterobacter cloacae (n=6, 5)	6	5		
Escherichia coli (n=6, 4)	5	4		
Klebsiella pneumoniae (n=16, 28)	14	25		
Pseudomonas aeruginosa (n=10, 13)	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically evaluable at EOT analysis set (pathogens in ≥5 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at end of treatment (EOT) visit in microbiologically evaluable at EOT analysis set (pathogens in ≥5 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the end of treatment (EOT) visit (within 24 hours after last IV dose)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	40		
Units: participants with favorable responses				
Enterobacter aerogenes (n=4, 2)	3	2		
Enterobacter cloacae (n=6, 5)	6	5		
Escherichia coli (n=5, 4)	5	4		
Klebsiella pneumoniae (n=16, 26)	14	23		
Pseudomonas aeruginosa (n=4, 6)	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set at TOC visit (pathogens in ≥5 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set at TOC visit (pathogens in ≥5 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	54		
Units: participants with favorable responses				
Enterobacter aerogenes (n=4, 2)	3	2		
Enterobacter cloacae (n=6, 6)	5	5		
Escherichia coli (n=6, 5)	4	4		
Klebsiella pneumoniae (n=20, 30)	15	18		
Pseudomonas aeruginosa (n=11, 15)	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in extended microbiologically evaluable at TOC analysis set (pathogens in ≥5 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in extended microbiologically evaluable at TOC analysis set (pathogens in ≥5 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	41		
Units: participants with favorable responses				
Enterobacter cloacae (n=5, 5)	4	4		
Escherichia coli (n=5, 4)	4	4		
Klebsiella pneumoniae (n=14, 22)	11	14		
Pseudomonas aeruginosa (n=9, 13)	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically evaluable at TOC analysis set (pathogens in ≥5 patients)

End point title	The proportion of favorable per-pathogen microbiologic responses in patients with pathogens resistant to ceftazidime at test-of-cure (TOC) visit in microbiologically evaluable at TOC analysis set (pathogens in ≥5 patients)

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favorable microbiological response includes: Eradication where, source specimen demonstrates absence of the original baseline pathogen. Presumed eradication where, source specimen was not available to culture and the patient was assessed as a clinical cure.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: participants with favorable responses				
Enterobacter cloacae (n=5, 5)	4	4		
Escherichia coli (n=4, 4)	4	4		

Klebsiella pneumoniae (n=14, 20)	11	13		
Pseudomonas aeruginosa (n=3, 6)	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with death due to any cause (all-cause mortality) at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set at test-of-cure visit

End point title	The proportion of patients with death due to any cause (all-cause mortality) at test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set at test-of-cure visit

End point description:

The proportion of patients with death due to any cause (all-cause mortality) in microbiologically modified intent-to-treat analysis set at test-of-cure visit.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
Number of patients who died (all cause mortality)	16	14		
Deaths due to disease progression	6	5		
Number of patients with any AE with outcome=death	10	9		
Number of patients alive	153	170		
Number of patients with unknown survival status	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with death due to any cause (all-cause mortality) at test-of-cure (TOC) visit in clinically modified intent-to-treat analysis set at test-of-cure visit

End point title	The proportion of patients with death due to any cause (all-cause mortality) at test-of-cure (TOC) visit in clinically modified intent-to-treat analysis set at test-of-cure visit

End point description:

The proportion of patients with death due to any cause (all-cause mortality) in clinically modified intent-to-treat analysis set at test-of-cure visit.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	370		
Units: participants				
Number of patients who died (all cause mortality)	29	25		
Deaths due to disease progression	10	6		
Number of patients with any AE with outcome=death	19	19		
Number of patients alive	316	341		
Number of patients with unknown survival status	11	4		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with death due to any cause (all-cause mortality) at test-of-cure (TOC) visit in the clinically evaluable at test-of-cure analysis set

End point title	The proportion of patients with death due to any cause (all-cause mortality) at test-of-cure (TOC) visit in the clinically evaluable at test-of-cure analysis set

End point description:

The proportion of patients with death due to any cause (all-cause mortality) in the clinically evaluable at test-of-cure analysis set.

End point type	Secondary

End point timeframe:

At the test-of-cure (TOC) visit (Day 21 to 25)

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	270		
Units: participants				
Number of patients who died (all cause mortality)	11	8		
Deaths due to disease progression	5	4		
Number of patients with any AE with outcome=death	6	4		
Number of patients alive	245	262		
Number of patients with unknown survival status	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with death due to any cause (all-cause mortality) in microbiologically modified intent-to-treat analysis set at day 28

End point title	The proportion of patients with death due to any cause (all-cause mortality) in microbiologically modified intent-to-treat analysis set at day 28

End point description:

The proportion of patients with death due to any cause (all-cause mortality) in microbiologically modified intent-to-treat analysis set at day 28.

End point type	Secondary

End point timeframe:

at Day 28 from randomization

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
Number of patients who died (all cause mortality)	17	16		
Deaths due to disease progression	6	5		
Number of patients with any AE with outcome=death	11	11		
Number of patients alive	152	168		
Number of patients with unknown survival status	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with death due to any cause (all-cause mortality) in clinically modified intent-to-treat analysis set at day 28

End point title	The proportion of patients with death due to any cause (all-cause mortality) in clinically modified intent-to-treat analysis set at day 28

End point description:

The proportion of patients with death due to any cause (all-cause mortality) in clinically modified intent-to-treat analysis set at day 28.

End point type	Secondary

End point timeframe:

at Day 28 from randomization

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	370		
Units: participants				
Number of patients who died (all cause mortality)	30	27		
Deaths due to disease progression	10	6		
Number of patients with any AE with outcome=death	20	21		
Number of patients alive	315	339		
Number of patients with unknown survival status	11	4		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients with death due to any cause (all-cause mortality) in the clinically evaluable at test-of-cure analysis set at day 28

End point title	The proportion of patients with death due to any cause (all-cause mortality) in the clinically evaluable at test-of-cure analysis set at day 28

End point description:

The proportion of patients with death due to any cause (all-cause mortality) in the clinically evaluable at test-of-cure analysis set at day 28.

End point type	Secondary

End point timeframe:

at Day 28 from randomization

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	270		
Units: participants				
Number of patients who died (all cause mortality)	12	9		
Deaths due to disease progression	5	4		
Number of patients with any AE with outcome=death	7	5		
Number of patients alive	244	261		
Number of patients with unknown survival status	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients discharged from hospital up to test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set

End point title	The proportion of patients discharged from hospital up to test-of-cure (TOC) visit in microbiologically modified intent-to-treat analysis set

End point description:

The proportion of patients discharged from hospital in microbiologically modified intent-to-treat analysis set.

End point type	Secondary

End point timeframe:

up to 25 days from randomization

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	184		
Units: participants				
Number of patients with admission date	170	182		
Number of patients with at least one discharge	71	75		
1 discharge	71	74		
2 discharges	0	1		
>2 discharges	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients discharged from hospital up to test-of-cure (TOC) visit in the clinically modified intent-to-treat analysis set

End point title	The proportion of patients discharged from hospital up to test-of-cure (TOC) visit in the clinically modified intent-to-treat analysis set

End point description:

The proportion of patients discharged from hospital in the clinically modified intent-to-treat analysis set.

End point type	Secondary

End point timeframe:

up to 25 days from randomization

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	370		
Units: participants				
Number of patients with admission date	355	366		
Number of patients with at least one discharge	206	206		
1 discharge	201	200		
2 discharges	5	4		
>2 discharges	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients discharged from hospital up to test-of-cure (TOC) visit in the clinically evaluable at test-of-cure analysis set

End point title	The proportion of patients discharged from hospital up to test-of-cure (TOC) visit in the clinically evaluable at test-of-cure analysis set

End point description:

The proportion of patients discharged from hospital in the clinically evaluable at test-of-cure analysis set.

End point type	Secondary

End point timeframe:

up to 25 days from randomization

End point values	CAZ-AVI	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	270		
Units: participants				
Number of patients with admission date	256	266		
Number of patients with at least one discharge	148	155		
1 discharge	144	151		
2 discharges	4	3		
>2 discharges	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Nonserious AEs and SAEs were collected for each patient from the time when informed consent was obtained at Screening (Day –1 to 0) through the final protocol follow-up (FPFU) visit.

Adverse event reporting additional description:

AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study center personnel, or revealed by observation were to be collected and recorded in the eCRF. Please note: "The section "total # of deaths resulting from adverse events" is for fatalities that are causally related to the treatment".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Meropenem

Reporting group description:

meropenem 1000mg IV infused over 30 minutes plus CAZ-AVI placebo. Total # Subjects Affected by Non Serious Adverse Events (with preferred terms meeting frequency threshold)

Reporting group title	CAZ-AVI

Reporting group description:

2000mg ceftazidime / 500mg avibactam intravenous (IV) infused over 2 hours plus appropriate placebo to meropenem. Total # Subjects Affected by Non Serious Adverse Events (with preferred terms meeting frequency threshold)

Serious adverse events	Meropenem	CAZ-AVI	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 403 (13.40%)	75 / 405 (18.52%)	
number of deaths (all causes)	30	38	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchioloalveolar carcinoma			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal cancer metastatic			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive emergency			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 403 (0.25%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 403 (0.25%)	3 / 405 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Intentional medical device removal by patient			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multi-organ failure			
subjects affected / exposed	1 / 403 (0.25%)	3 / 405 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 403 (0.00%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute respiratory failure			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
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 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial secretion retention			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Bronchoplegia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 403 (0.00%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	3 / 403 (0.74%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 403 (0.25%)	4 / 405 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	3 / 403 (0.74%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 403 (0.00%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	4 / 403 (0.99%)	5 / 405 (1.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 5	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weaning failure			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 403 (0.25%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 403 (0.74%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac asthma			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 403 (0.74%)	4 / 405 (0.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 3	
Cardiac failure acute			
subjects affected / exposed	2 / 403 (0.50%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 403 (0.00%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			

subjects affected / exposed	2 / 403 (0.50%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cyanosis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
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	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexopathy			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	2 / 403 (0.50%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	1 / 403 (0.25%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (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 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subacute hepatic failure			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 403 (0.25%)	2 / 405 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myopathy			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
CNS ventriculitis			
subjects affected / exposed	1 / 403 (0.25%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	2 / 403 (0.50%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter pneumonia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

HIV infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 403 (1.49%)	7 / 405 (1.73%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 403 (0.25%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 403 (0.99%)	5 / 405 (1.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	3 / 403 (0.74%)	3 / 405 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Tracheitis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (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 / 403 (0.25%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 403 (0.00%)	1 / 405 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 403 (0.25%)	0 / 405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Meropenem	CAZ-AVI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	195 / 403 (48.39%)	198 / 405 (48.89%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 403 (4.71%)	16 / 405 (3.95%)	
occurrences (all)	20	16	
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 403 (4.22%)	16 / 405 (3.95%)	
occurrences (all)	18	16	
Vascular disorders			

Hypertension			
subjects affected / exposed	15 / 403 (3.72%)	14 / 405 (3.46%)	
occurrences (all)	16	14	
Hypotension			
subjects affected / exposed	8 / 403 (1.99%)	10 / 405 (2.47%)	
occurrences (all)	13	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 403 (4.47%)	24 / 405 (5.93%)	
occurrences (all)	21	25	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	15 / 403 (3.72%)	17 / 405 (4.20%)	
occurrences (all)	15	18	
Pyrexia			
subjects affected / exposed	13 / 403 (3.23%)	10 / 405 (2.47%)	
occurrences (all)	20	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 403 (1.99%)	10 / 405 (2.47%)	
occurrences (all)	8	11	
Constipation			
subjects affected / exposed	31 / 403 (7.69%)	25 / 405 (6.17%)	
occurrences (all)	38	25	
Diarrhoea			
subjects affected / exposed	62 / 403 (15.38%)	60 / 405 (14.81%)	
occurrences (all)	68	65	
Nausea			
subjects affected / exposed	7 / 403 (1.74%)	13 / 405 (3.21%)	
occurrences (all)	7	13	
Vomiting			
subjects affected / exposed	22 / 403 (5.46%)	23 / 405 (5.68%)	
occurrences (all)	24	28	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	7 / 403 (1.74%)	9 / 405 (2.22%)	
occurrences (all)	7	10	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	6 / 403 (1.49%)	9 / 405 (2.22%)	
occurrences (all)	6	13	
Rash			
subjects affected / exposed	13 / 403 (3.23%)	8 / 405 (1.98%)	
occurrences (all)	13	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 403 (2.73%)	4 / 405 (0.99%)	
occurrences (all)	11	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	14 / 403 (3.47%)	11 / 405 (2.72%)	
occurrences (all)	14	11	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	33 / 403 (8.19%)	43 / 405 (10.62%)	
occurrences (all)	40	47	
Hyponatraemia			
subjects affected / exposed	6 / 403 (1.49%)	10 / 405 (2.47%)	
occurrences (all)	6	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2014	1. Clarification of the visit structure and timing of visit and assessments
29 September 2014	1. Amendment of exclusion criteria with respect to moderate and severe renal impairment with estimated creatinine clearance (CrCl) ≤50 ml/min
09 January 2015	1. Re-introducing the inclusion of patients with renal impairment (creatinine clearance (CrCl) ≤ 50 ml/min).
25 September 2015	1. Changes to statistical methods and overall sample size of approximately 850 patients

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 September 2014	There was an interruption to recruitment of moderate or severe renal impairment at baseline patients whilst a new dosing regimen was agreed.	13 January 2015

Notes:

Limitations and caveats

None reported