Clinical trial results:
An Open-Label, Randomized, Multicenter, Phase III Study of Ceftazidime-Avibactam (CAZ-AVI, formerly CAZ104) and Best Available Therapy for the Treatment of Infections Due to Ceftazidime Resistant Gram-Negative Pathogens

Summary

EudraCT number	2012-000726-21
Trial protocol	BE DE CZ ES GR BG HU IT GB
Global end of trial date	29 September 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	27 April 2016

Trial information

Trial identification

Sponsor protocol code	D4280C00006

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	151 85 Södertälje, Södertälje, Sweden,
Public contact	Nell Moore, AstraZeneca, UK 44 788-411-5907, Nell.Moore@astrazeneca.com
Scientific contact	Leanne Gasink, AstraZeneca, USA 302-885-5550, Leanne.Gasink@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	19 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2014
Global end of trial reached?	Yes
Global end of trial date	29 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the per-patient clinical response to ceftazidime-avibactam (CAZ-AVI, formerly CAZ104) and Best Available Therapy (BAT) at Test of Cure (TOC) in the treatment of selected serious infections caused by ceftazidime-resistant Gram-negative pathogens.

Protection of trial subjects:

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1): Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 91
Country: Number of subjects enrolled	Croatia: 12
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Romania: 31
Country: Number of subjects enrolled	Russian Federation: 74
Country: Number of subjects enrolled	Turkey: 23
Country: Number of subjects enrolled	Ukraine: 31
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	South Africa: 2

Worldwide total number of subjects	333
EEA total number of subjects	147

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)	159
From 65 to 84 years	163
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

A total of 333 patients were randomized in 53 centers in 16 countries: 306 patients had cUTI and 27 patients had cIAI. The first patient was randomized on 07 January 2013 and the last patient was randomized on 29 August 2014. One patient in the CAZ-AVI arm was randomized but did not receive study drug.

Pre-assignment

Screening details:

None

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	cIAI:Best Available Therapy

Arm description:

cIAI: Best Available Therapy Determinated by Investigator

Arm type	Active comparator
Investigational medicinal product name	Investigator-determined BAT(protocol preferred BAT options: meropenem,imipenem,doripenem,tigecycline, and colistin (if colistin,metronidazole should be added)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Details for dose and frequency of administration of BAT can be found.

Arm title	cIAI:CAZ-AVI + metronidazole

Arm description:

cIAI:CAZ-AVI (2000 mg ceftazidime/500 mg avibactam) plus metronidazole (500 mg)

Arm type	Experimental
Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Metronidazole 500 mg/100 mL solution for infusion

Investigational medicinal product name	CAZ-AVI (single-vial product supply)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Sterile crystalline powder, 2000 mg ceftazidime/500 mg avibactam for solution for infusion

Arm title	cUTI:Best Available Therapy
Arm description: cUTI:Best Available Therapy Determinated by Investigator	
Arm type	Active comparator
Investigational medicinal product name	Investigator-determined BAT(protocol preferred BAT options: meropenem,imipenem,doripenem,tigecycline, and colistin (if colistin,metronidazole should be added)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Details for dose and frequency of administration of BAT can be found.	

Arm title	cUTI:CAZ-AVI
Arm description: cUTI: CAZ-AVI	
Arm type	Experimental
Investigational medicinal product name	CAZ-AVI (single-vial product supply)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Sterile crystalline powder, 2000 mg ceftazidime/500 mg avibactam for	

Number of subjects in period 1	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy
Started	15	12	153
Completed	13	12	148
Not completed	2	0	5
Adverse event, serious fatal	1	-	3
Consent withdrawn by subject	1	-	2
Other Eligibility criteria	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	cUTI:CAZ-AVI
Started	153
Completed	143
Not completed	10
Adverse event, serious fatal	3
Consent withdrawn by subject	1
Other Eligibility criteria	2
Lost to follow-up	4

Baseline characteristics

Reporting groups	
Reporting group title	cIAI:Best Available Therapy
Reporting group description:	
cIAI: Best Available Therapy Determinated by Investigator	
Reporting group title	cIAI:CAZ-AVI + metronidazole
Reporting group description:	
cIAI:CAZ-AVI (2000 mg ceftazidime/500 mg avibactam) plus metronidazole (500 mg)	
Reporting group title	cUTI:Best Available Therapy
Reporting group description:	
cUTI:Best Available Therapy Determinated by Investigator	
Reporting group title	cUTI:CAZ-AVI
Reporting group description:	
cUTI: CAZ-AVI	

Reporting group values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy
Number of subjects	15	12	153
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	10	79
From 65-84 years	7	2	71
85 years and over	1	0	3
Age Continuous | Units: Years			
arithmetic mean	59.5	50.3	61
standard deviation	± 18.78	± 14.71	± 15.27
Gender, Male/Female Units: Participants			
Female	5	7	73
Male	10	5	80
Age, Customized Units: Subjects			
18-45	3	3	24
46-64	4	7	55
65-74	4	2	46
75-90	4	0	28

Reporting group values	cUTI:CAZ-AVI	Total	
Number of subjects	153	333	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	63	159	
From 65-84 years	83	163	
85 years and over	7	11	
Age Continuous | Units: Years			
arithmetic mean	64.3		
standard deviation	± 14.72	-	
Gender, Male/Female Units: Participants			
Female	67	152	
Male	86	181	
Age, Customized Units: Subjects			
18-45	20	50	
46-64	43	109	
65-74	50	102	
75-90	40	72	

End points

End points reporting groups

Reporting group title	cIAI:Best Available Therapy
Reporting group description: cIAI: Best Available Therapy Determinated by Investigator	
Reporting group title	cIAI:CAZ-AVI + metronidazole
Reporting group description: cIAI:CAZ-AVI (2000 mg ceftazidime/500 mg avibactam) plus metronidazole (500 mg)	
Reporting group title	cUTI:Best Available Therapy
Reporting group description: cUTI:Best Available Therapy Determinated by Investigator	
Reporting group title	cUTI:CAZ-AVI
Reporting group description: cUTI: CAZ-AVI	

Primary: Clinical response at Test of Cure (TOC) in Microbiological modified intent-to-treat (mMITT) analysis set

End point title	Clinical response at Test of Cure (TOC) in Microbiological modified intent-to-treat (mMITT) analysis set[1]

End point description:

Proportion of patients with clinical cure at the TOC visit in the mMITT analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Primary

End point timeframe:

6-12 days after last infusion of study therapy

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No treatment comparisons were done in this study. No no statistical analysis section were entered.

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
Clinical cure	6	8	129	132
Clinical failure	0	0	2	2
Indeterminate	5	2	6	10

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at End of treatment (EOT) in mMITT analysis set.

End point title	Clinical response at End of treatment (EOT) in mMITT analysis set.

End point description:

Proportion of patients with clinical cure at the EOT visit in the mMITT analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

28 hours after completion of last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
Clinical cure	6	9	136	142
Clinical failure	0	0	0	0
Indeterminate	5	1	1	2

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at Follow-up 1 (FU1) in mMITT analysis set

End point title	Clinical response at Follow-up 1 (FU1) in mMITT analysis set

End point description:

Proportion of patients with clinical cure at the FU1 visit in the mMITT analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

cIAI: 27-37 calendar days from randomization/cUTI: 20-27 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
Clinical cure	6	8	121	127
Clinical failure	0	0	8	5

Indeterminate	5	2	8	12

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at Follow-up 2 (FU2) in mMITT analysis set

End point title	Clinical response at Follow-up 2 (FU2) in mMITT analysis set

End point description:

Proportion of patients with clinical cure at the FU2 visit in the mMITT analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

cUTI only: 28-34 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	137	144
Units: Participant				
Clinical cure			118	123
Clinical failure			13	11
Indeterminate			6	10

Notes:

[2] - cIAI patients: FU2 is not applicable.

[3] - cIAI patients: FU2 is not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at EOT in Extended Microbiologically Evaluable (EME) at EOT analysis set.

End point title	Clinical response at EOT in Extended Microbiologically Evaluable (EME) at EOT analysis set.

End point description:

Proportion of patients with clinical cure at the EOT visit in the EME at EOT analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

28 hours after completion of last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	9	127	134
Units: Participant				
Clinical cure	5	9	127	134
Clinical failure	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at TOC in EME at TOC analysis set.

End point title	Clinical response at TOC in EME at TOC analysis set.

End point description:

Proportion of patients with clinical cure at the TOC visit in the EME at TOC analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	122	128
Units: Participant				
Clinical cure	5	8	120	126
Clinical failure	0	0	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at FU1 in EME at FU1 analysis set.

End point title	Clinical response at FU1 in EME at FU1 analysis set.

End point description:

Proportion of patients with clinical cure at the FU1 visit in EME at FU1 analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that

no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

cIAI: 27-37 calendar days from randomization/cUTI: 20-27 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	118	124
Units: Participant				
Clinical cure	5	7	110	120
Clinical failure	0	0	8	4

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response at FU2 in EME at FU2 analysis set

End point title	Clinical response at FU2 in EME at FU2 analysis set

End point description:

Proportion of patients with clinical cure at the FU2 visit in EME at FU2 analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary.

End point type	Secondary

End point timeframe:

cUTI only: 28-34 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[4]	0[5]	114	116
Units: Participant				
Clinical cure			102	106
Clinical failure			12	10

Notes:

[4] - cIAI patients: FU2 is not applicable.

[5] - cIAI patients: FU2 is not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at TOC by baseline Gram-negative pathogen in mMITT analysis set

End point title	Clinical cure at TOC by baseline Gram-negative pathogen in mMITT analysis set

End point description:

Proportion of patients with clinical cure at TOC visit by baseline pathogen (>=10% of frequncy in the combined cIAI and cUTI patients) in the mMITT analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
E. coli - Clinical cure (n=6, 4, 57, 59)	2	3	54	53
K. pneumoniae - Clinical cure (n=3, 5, 65, 55)	2	3	61	54
P. aeruginosa - clinical cure (n=1, 1, 5, 14)	1	1	5	12

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at TOC by baseline Gram-negative pathogen in EME at TOC analysis set

End point title	Clinical cure at TOC by baseline Gram-negative pathogen in EME at TOC analysis set

End point description:

Proportion of patients with clinical cure at TOC visit by baseline Gram-negative pathogen (>=10% of frequncy in the combined cIAI and cUTI patients) in EME at TOC analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	124	131
Units: Participant				
E. coli - Clinical cure (n=2, 3, 48, 52)	2	3	47	51
K. pneumoniae - Clinical cure (n=2, 3, 59, 53)	2	3	59	53
P. aeruginosa - Clinical cure (n=1, 1, 5, 12)	1	1	5	12

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at TOC by previously failed treatment class in mMITT analysis set

End point title	Clinical cure at TOC by previously failed treatment class in mMITT analysis set

End point description:

Proportion of patients with clinical cure at TOC visit by previously failed treatment class in the mMITT analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
At least 1 failed - Cure (n=4,7,12,7)	3	7	12	6
Antibiotics - Cure (n=0,1,0,0)	0	1	0	0
Carbapenems - Cure (n=1,0,1,2)	0	0	1	1
Comb of Sulf/Trime inc Deriv-Cure(n=0,0,2,0)	0	0	2	0
Combs Of Peni. Inc B-Lact. Inhib.-Cure(n=1,3,0,2)	1	3	0	2
Cortico,Po. Comb W/Antibio.-Cure(n=0,0,1,0)	0	0	1	0
First-Gen. Cephalosporins-Cure (n=0,0,2,0)	0	0	2	0
Fluoroquinolones - Cure (n=1,2,7,1)	0	2	7	1
Glycopeptide Antibacterials-Cure (n=1,0,0,0)	0	0	0	0
Imidazole Derivatives - Cure (n=2,3,0,0)	1	3	0	0

Other Aminoglycosides-Cure (n=0,0,1,1)	0	0	1	1
Other Antibacterials-Cure (n=0,1,1,0)	0	1	1	0
Other Antibio. F. Topic. Use-Cure(n=0,0,1,0)	0	0	1	0
Penici. With Ext. Spectrum-Cure(n=0,1,0,0)	0	1	0	0
Third-Gen.Cephalosporins - Cure(n=2,4,3,2)	2	4	3	2

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at EOT by previously failed treatment class in EME at EOT analysis set

End point title	Clinical cure at EOT by previously failed treatment class in EME at EOT analysis set

End point description:

Proportion of patients with clinical cure at EOT visit by previously failed treatment class in EME at EOT analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

28 hours after completion of last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	9	127	134
Units: Participant				
Antibiotics - Cure (n=0,1,0,0)	0	1	0	0
Carbapenems - Cure (n=0,0,1,1)	0	0	1	1
Comb of Sulf/Trime inc Deriv-Cure(n=0,0,2,0)	0	0	2	0
Combs Of Peni. Inc B-Lact. Inhib.-Cure(n=1,3,0,2)	1	3	0	2
Cortico,Po. Comb W/Antibio.-Cure(n=0,0,1,0)	0	0	1	0
First-Gen. Cephalosporins-Cure (n=0,0,2,0)	0	0	2	0
Fluoroquinolones - Cure (n=0,2,5,1)	0	2	5	1
Imidazole Derivatives - Cure (n=1,3,0,0)	1	3	0	0
Other Aminoglycosides-Cure (n=0,0,1,1)	0	0	1	1
Other Antibacterials-Cure (n=0,1,1,0)	0	1	1	0
Other Antibio. F. Topic. Use-Cure(n=0,0,1,0)	0	0	1	0

Penici. With Ext. Spectrum-Cure(n=0,1,0,0)	0	1	0	0
Third-Gen.Cephalosporins - Cure(n=2,4,2,2)	2	4	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at TOC by previously failed treatment class in EME at TOC analysis set

End point title	Clinical cure at TOC by previously failed treatment class in EME at TOC analysis set

End point description:

Proportion of patients with clinical cure at TOC visit by previously failed treatment class in EME at TOC analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	122	128
Units: Participant				
Antibiotics - Cure (n=0,1,0,0)	0	1	0	0
Carbapenems - Cure (n=0,0,1,1)	0	0	1	1
Comb of Sulf/Trime inc Deriv-Cure(n=0,0,2,0)	0	0	2	0
Combs Of Peni. Inc B-Lact. Inhib.-Cure(n=1,3,0,2)	1	3	0	2
Cortico,Po. Comb W/Antibio.-Cure(n=0,0,1,0)	0	0	1	0
First-Gen. Cephalosporins-Cure (n=0,0,2,0)	0	0	2	0
Fluoroquinolones - Cure (n=0,2,5,1)	0	2	5	1
Imidazole Derivatives - Cure (n=1,3,0,0)	1	3	0	0
Other Aminoglycosides-Cure (n=0,0,0,1)	0	0	0	1
Other Antibacterials-Cure (n=0,1,1,0)	0	1	1	0
Other Antibio. F. Topic. Use-Cure(n=0,0,1,0)	0	0	1	0
Penici. With Ext. Spectrum-Cure(n=0,1,0,0)	0	1	0	0
Third-Gen.Cephalosporins - Cure(n=2,4,2,2)	2	4	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at FU1 by previously failed treatment class in EME at FU1 analysis set

End point title	Clinical cure at FU1 by previously failed treatment class in EME at FU1 analysis set

End point description:

Proportion of patients with clinical cure at FU1 visit by previously failed treatment class in EME at FU1 analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary; for cIAI patients no drainage or surgical intervention after 96 hours from randomization is necessary (ie. drainage or surgical intervention up to 96 hours from randomization is permissible).

End point type	Secondary

End point timeframe:

cIAI: 27-37 calendar days from randomization/cUTI: 20-27 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	118	124
Units: Participant				
Antibiotics - Cure (n=0,1,0,0)	0	1	0	0
Carbapenems - Cure (n=0,0,1,1)	0	0	1	1
Comb of Sulf/Trime inc Deriv-Cure(n=0,0,1,0)	0	0	1	0
Combs Of Peni. Inc B-Lact. Inhib.-Cure(n=1,3,0,2)	1	3	0	2
Cortico,Po. Comb W/Antibio.-Cure(n=0,0,1,0)	0	0	0	0
First-Gen. Cephalosporins-Cure (n=0,0,2,0)	0	0	2	0
Fluoroquinolones - Cure (n=0,2,5,1)	0	2	4	1
Imidazole Derivatives - Cure (n=1,3,0,0)	1	3	0	0
Other Aminoglycosides-Cure (n=0,0,0,1)	0	0	0	1
Other Antibacterials-Cure (n=0,1,1,0)	0	1	1	0
Other Antibio. F. Topic. Use-Cure(n=0,0,1,0)	0	0	1	0
Penici. With Ext. Spectrum-Cure(n=0,1,0,0)	0	1	0	0
Third-Gen.Cephalosporins - Cure(n=2,4,1,2)	2	4	0	2

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at FU2 by previously failed treatment class in EME at FU2 analysis set

End point title	Clinical cure at FU2 by previously failed treatment class in EME at FU2 analysis set

End point description:

Proportion of patients with clinical cure at FU2 visit by previously failed treatment class in EME at FU2 analysis set. Clinical cure: Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy (other than those allowed per protocol) is necessary.

End point type	Secondary

End point timeframe:

cUTI only: 28-34 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	114	116
Units: Participant				
Carbapenems - Cure (n=1,0)			0	0
Comb of Sulf/Trime inc Deriv-Cure(n=1,0)			0	0
Combs Of Peni. Inc B-Lact. Inhib.-Cure(n=0,2)			0	2
Cortico,Po. Comb W/Antibio.-Cure(n=1,0)			0	0
First-Gen. Cephalosporins-Cure (n=2,0)			2	0
Fluoroquinolones - Cure (n=5,0)			4	0
Other Aminoglycosides-Cure (n=0,1)			0	1
Other Antibacterials-Cure (n=1,0)			0	0
Other Antibio. F. Topic. Use-Cure(n=1,0)			1	0
Third-Gen.Cephalosporins -Cure(n=1,1)			0	1

Notes:

[6] - cIAI patients: FU2 is not applicable.

[7] - cIAI patients: FU2 is not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at EOT in mMITT analysis set

End point title	Per-patient microbiological response at EOT in mMITT analysis set

End point description:

Microbiological responses as per the protocoled criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cIAI patients where the clinical response was changed to indeterminate due to a Surgical Review Panel assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

End point type	Secondary

End point timeframe:

28 hours after completion of last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
Favorable	6	9	130	136
Unfavorable	0	0	1	1
Indeterminate	5	1	6	7

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at TOC in mMITT analysis set

End point title	Per-patient microbiological response at TOC in mMITT analysis set

End point description:

Microbiological responses as per the protocoled criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cIAI patients where the clinical response was changed to indeterminate due to a Surgical Review Panel assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
Favorable	6	8	88	118
Unfavorable	0	0	42	17
Indeterminate	5	2	7	9

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at FU1 in mMITT analysis set

End point title	Per-patient microbiological response at FU1 in mMITT analysis set

End point description:

Microbiological responses as per the protocoled criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cIAI patients where the clinical response was changed to indeterminate due to a Surgical Review Panel assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

End point type	Secondary

End point timeframe:

cUTI: 20-27 calendar days from randomization/cIAI: 27-37 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
Favorable	6	8	78	103
Unfavorable	0	0	50	29
Indeterminate	5	2	9	12

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at FU2 in mMITT analysis set

End point title	Per-patient microbiological response at FU2 in mMITT analysis set

End point description:

Microbiological responses as per the protocoled criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cIAI patients where the clinical response was changed to indeterminate due to a Surgical Review Panel assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

End point type	Secondary

End point timeframe:

cUTI only: 28-34 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[8]	0[9]	137	144
Units: Participant				
Favorable			73	99
Unfavorable			54	35
Indeterminate			10	10

Notes:

[8] - cIAI patients: FU2 is not applicable.

[9] - cIAI patients: FU2 is not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at EOT in EME at EOT analysis set

End point title	Per-patient microbiological response at EOT in EME at EOT analysis set

End point description:

Microbiological responses as per the protocoled criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cIAI patients where the clinical response was changed to indeterminate due to a Surgical Review Panel assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

End point type	Secondary

End point timeframe:

28 hours after completion of last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	9	127	134
Units: Participant				
Favorable	5	9	127	133
Unfavorable	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at TOC in EME at TOC analysis set

End point title	Per-patient microbiological response at TOC in EME at TOC analysis set

End point description:

Microbiological responses as per the protocoled criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cIAI patients where the clinical response was changed to indeterminate due to a Surgical Review Panel assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	124	131
Units: Participant				
Favorable	5	8	84	114
Unfavorable	0	0	40	17

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at FU1 in EME at FU1 analysis set

End point title	Per-patient microbiological response at FU1 in EME at FU1 analysis set

End point description:

Microbiological responses as per the protocoled criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included

"eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cIAI patients where the clinical response was changed to indeterminate due to a Surgical Review Panel assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

End point type	Secondary

End point timeframe:

cUTI: 20-27 calendar days from randomization/cIAI: 27-37 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	120	126
Units: Participant				
Favorable	5	7	75	98
Unfavorable	0	0	45	28

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at FU2 in EME at FU2 analysis set

End point title	Per-patient microbiological response at FU2 in EME at FU2 analysis set

End point description:

Microbiological responses as per the protocoled criteria: responses other than "indeterminate" were classified as "favorable" or "unfavorable." Favorable microbiological response assessments included "eradication" and "presumed eradication." Unfavorable microbiological response assessments included "persistence," "persistence with increasing minimum inhibitory concentration (MIC)," and "presumed persistence." Indeterminate microbiologic response assessments included cIAI patients where the clinical response was changed to indeterminate due to a Surgical Review Panel assessment of inadequate source control (ie, circumstances that preclude classification as eradication, presumed eradication, persistence, persistence with increasing MIC, and presumed persistence).

End point type	Secondary

End point timeframe:

cUTI only: 28-34 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[10]	0[11]	115	117
Units: Participant				
Favorable			68	85
Unfavorable			47	32

Notes:

[10] - cIAI patients: FU2 is not applicable.

[11] - cIAI patients: FU2 is not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at EOT in mMITT analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at EOT in mMITT analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

28 hours after completion of last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
E. coli - Favorable (n=6, 4, 57, 59)	2	3	53	57
E. coli - Unfavorable (n=6, 4, 57, 59)	0	0	0	0
E. coli - Indeterminate (n=6, 4, 57, 59)	4	1	4	2
K. pneumoniae - Favorable (n=3, 5, 65, 55)	2	4	61	52
K. pneumoniae - Unfavorable (n=3, 5, 65, 55)	0	0	1	0
K. pneumoniae - Indeterminate (n=3, 5, 65, 55)	1	1	3	3
P. aeruginosa - Favorable (n=1, 1, 5, 14)	1	1	5	14
P. aeruginosa - Unfavorable (n=1, 1, 5, 14)	0	0	0	0
P. aeruginosa - Indeterminate (n=1, 1, 5, 14)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at TOC in mMITT analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at TOC in mMITT analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
E. coli - Favorable (n=6, 4, 57, 59)	2	3	38	52
E. coli - Unfavorable (n=6, 4, 57, 59)	0	0	16	3
E. coli - Indeterminate (n=6, 4, 57, 59)	4	1	3	4
K. pneumoniae - Favorable (n=3, 5, 65, 55)	2	3	43	46
K. pneumoniae - Unfavorable (n=3, 5, 65, 55)	0	0	19	8
K. pneumoniae - Indeterminate (n=3, 5, 65, 55)	1	2	3	1
P. aeruginosa - Favorable (n=1, 1, 5, 14)	1	1	3	11
P. aeruginosa - Unfavorable (n=1, 1, 5, 14)	0	0	2	2
P. aeruginosa - Indeterminate (n=1, 1, 5, 14)	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at FU1 in mMITT analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at FU1 in mMITT analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen

from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

cIAI: 27-37 calendar days from randomization/cUTI: 20-27 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
E. coli - Favorable (n=6, 4, 57, 59)	2	3	33	45
E. coli - Unfavorable (n=6, 4, 57, 59)	0	0	18	12
E. coli - Indeterminate (n=6, 4, 57, 59)	4	1	6	2
K. pneumoniae - Favorable (n=3, 5, 65, 55)	2	3	39	42
K. pneumoniae - Unfavorable (n=3, 5, 65, 55)	0	0	23	10
K. pneumoniae - Indeterminate (n=3, 5, 65, 55)	1	2	3	3
P. aeruginosa - Favorable (n=1, 1, 5, 14)	1	1	3	8
P. aeruginosa - Unfavorable (n=1, 1, 5, 14)	0	0	2	2
P. aeruginosa - Indeterminate (n=1, 1, 5, 14)	0	0	0	4

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at FU2 in mMITT analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at FU2 in mMITT analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

cUTI only: 28-34 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[12]	0[13]	137	144
Units: Participant				
E. coli - Favorable (n=0, 0, 57, 59)			32	43
E. coli - Unfavorable (n=0, 0, 57, 59)			19	14
E. coli - Indeterminate (n=0, 0, 57, 59)			6	2
K. pneumoniae - Favorable (n=0, 0, 65, 55)			35	39
K. pneumoniae - Unfavorable (n=0, 0, 65, 55)			26	14
K. pneumoniae - Indeterminate (n=0, 0, 65, 55)			4	2
P. aeruginosa - Favorable (n=0, 0, 5, 14)			2	10
P. aeruginosa - Unfavorable (n=0, 0, 5, 14)			3	2
P. aeruginosa - Indeterminate (n=0, 0, 5, 14)			0	2

Notes:

[12] - cIAI patients: FU2 is not applicable.

[13] - cIAI patients: FU2 is not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at EOT in EME at EOT analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at EOT in EME at EOT analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

28 hours after completion of last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	9	127	134
Units: Participant				
E. coli - Favorable (n=2, 3, 51, 55)	2	3	51	55
E. coli - Unfavorable (n=2, 3, 51, 55)	0	0	0	0
K. pneumoniae - Favorable (n=2, 4, 60, 52)	2	4	60	52
K. pneumoniae - Unfavorable (n=2, 4, 60, 52)	0	0	0	0
P. aeruginosa - Favorable (n=1, 1, 5, 14)	1	1	5	14
P. aeruginosa - Unfavorable (n=1, 1, 5, 14)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at TOC in EME at TOC analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at TOC in EME at TOC analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	124	131
Units: Participant				
E. coli - Favorable (n=2, 3, 49, 53)	2	3	34	50
E. coli - Unfavorable (n=2, 3, 49, 53)	0	0	15	3
K. pneumoniae - Favorable (n=2, 3, 60, 53)	2	3	42	45
K. pneumoniae - Unfavorable (n=2, 3, 60, 53)	0	0	18	8
P. aeruginosa - Favorable (n=1, 1, 5, 13)	1	1	3	11

P. aeruginosa - Unfavorable (n=1, 1, 5, 13)	0	0	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at FU1 in EME at FU1 analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at FU1 in EME at FU1 analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

cIAI: 27-37 calendar days from randomization/cUTI: 20-27 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	120	126
Units: Participant				
E. coli - Favorable (n=2, 3, 46, 54)	2	3	30	43
E. coli - Unfavorable (n=2, 3, 46, 54)	0	0	16	11
K. pneumoniae - Favorable (n=2, 2, 59, 50)	2	2	38	40
K. pneumoniae - Unfavorable (n=2, 2, 59, 50)	0	0	21	10
P. aeruginosa - Favorable (n=1, 1, 5, 10)	1	1	3	8
P. aeruginosa - Unfavorable (n=1, 1, 5, 10)	0	0	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at FU2 in EME at FU2 analysis set

End point title	Per-pathogen microbiological response of Gram-negative

	pathogen at FU2 in EME at FU2 analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

cUTI only: 28-34 calendar days from randomization

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[14]	0[15]	115	117
Units: Participant				
E. coli - Favorable (n=44, 50)			28	39
E. coli - Unfavorable (n=44, 50)			16	11
K. pneumoniae - Favorable (n= 56, 46)			33	32
K. pneumoniae - Unfavorable (n=56, 46)			23	14
P. aeruginosa - Favorable (n=4, 11)			2	9
P. aeruginosa - Unfavorable (n=4, 11)			2	2

Notes:

[14] - cIAI patients: FU2 is not applicable.

[15] - cIAI patients: FU2 is not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at TOC by CAZ-AVI MIC in mMITT analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at TOC by CAZ-AVI MIC in mMITT analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
E. coli (MIC: <=0.008)-Favorable (n=0, 0, 1, 1)	0	0	1	1
E. coli (MIC: 0.03)-Favorable (n=0, 0, 0, 2)	0	0	0	1
E. coli (MIC: 0.06)-Favorable (n=1, 0, 3, 2)	0	0	3	2
E. coli (MIC: 0.12)-Favorable (n=4, 2, 20, 20)	2	1	12	16
E. coli (MIC: 0.25)-Favorable (n=0, 0, 15, 16)	0	0	10	15
E. coli (MIC: 0.5)-Favorable (n=0, 1, 8, 11)	0	1	5	10
E. coli (MIC: 1)-Favorable (n=0, 0, 2, 2)	0	0	1	2
E. coli (MIC: 2)-Favorable (n=0, 0, 2, 1)	0	0	2	1
E. coli (MIC: 8)-Favorable (n=0, 0, 2, 4)	0	0	2	4
K. pneumoniae (MIC: 0.06)-Favorable (n=0,0,2,0)	0	0	1	0
K. pneumoniae (MIC: 0.12)-Favorable (n=0,1,8,5)	0	0	6	4
K. pneumoniae (MIC: 0.25)-Favorable (n=0,3,12,6)	0	2	7	5
K. pneumoniae (MIC: 0.5)-Favorable (n=2,0,24,22)	1	0	16	19
K. pneumoniae (MIC: 1)-Favorable (n=0,0,16,18)	0	0	11	16
K. pneumoniae (MIC: 2)-Favorable (n=1, 1, 1, 2)	1	1	1	1
K. pneumoniae (MIC: 4)-Favorable (n=0, 0, 1, 1)	0	0	1	0
K. pneumoniae (MIC: 32)-Favorable (n=0, 0, 1, 0)	0	0	0	0
K. pneumoniae (MIC: >32)-Favorable (n=0,0,0,1)	0	0	0	0
P. aeruginosa (MIC: 2)-Favorable (n=1, 0, 0, 1)	1	0	0	1
P. aeruginosa (MIC: 4)-Favorable (n=0, 0, 3, 2)	0	0	1	1
P. aeruginosa (MIC: 8)-Favorable (n=0, 0, 0, 2)	0	0	0	2
P. aeruginosa (MIC: 16)-Favorable (n=0, 1, 0, 1)	0	1	0	0
P. aeruginosa (MIC: 32)-Favorable (n=0, 0, 1, 3)	0	0	1	3
P. aeruginosa (MIC: >32)-Favorable (n=0,0,1,5)	0	0	1	4

Statistical analyses

No statistical analyses for this end point

Secondary: Per-pathogen microbiological response of Gram-negative pathogen at

TOC by CAZ-AVI MIC in EME at TOC analysis set

End point title	Per-pathogen microbiological response of Gram-negative pathogen at TOC by CAZ-AVI MIC in EME at TOC analysis set

End point description:

Proportion of patients with a favorable per-pathogen microbiological response for pathogens (>=10% of frequncy in the combined cIAI and cUTI patients): favourable microbiological response includes: Eradication Absence (or urine quantification < 10^4 CFU/ml for cUTI patients) of causative pathogen from an appropriately obtained specimen at the site of infection. If the patient was bacteremic at Screening, the bacteremia has also resolved. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure (specific to cIAI population).

End point type	Secondary

End point timeframe:

6-12 days after last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	124	131
Units: Participant				
E. coli (MIC: <=0.008)-Favorable (n=0, 0, 1, 1)	0	0	1	1
E. coli (MIC: 0.03)-Favorable (n=0, 0, 0, 2)	0	0	0	1
E. coli (MIC: 0.06)-Favorable (n=0, 0, 3, 1)	0	0	3	1
E. coli (MIC: 0.12)-Favorable (n=2, 1, 18, 18)	2	1	10	16
E. coli (MIC: 0.25)-Favorable (n=0, 0, 13, 15)	0	0	9	15
E. coli (MIC: 0.5)-Favorable (n=0, 1, 6, 9)	0	1	4	9
E. coli (MIC: 1)-Favorable (n=0, 0, 2, 2)	0	0	1	2
E. coli (MIC: 2)-Favorable (n=0, 0, 2, 1)	0	0	2	1
E. coli (MIC: 8)-Favorable (n=0, 0, 2, 4)	0	0	2	4
K. pneumoniae (MIC: 0.06)-Favorable (n=0,0,1,0)	0	0	0	0
K. pneumoniae (MIC: 0.12)-Favorable (n=0,0,8,5)	0	0	6	4
K. pneumoniae (MIC: 0.25)-Favorable (n=0,2,11,6)	0	2	7	5
K. pneumoniae (MIC: 0.5)-Favorable (n=1,0,23,21)	1	0	16	19
K. pneumoniae (MIC: 1)-Favorable (n=0,0,15,17)	0	0	11	15
K. pneumoniae (MIC: 2)-Favorable (n=1, 1, 1, 2)	1	1	1	2
K. pneumoniae (MIC: 4)-Favorable (n=0, 0, 1, 1)	0	0	1	0
K. pneumoniae (MIC: >32)-Favorable (n=0,0,0,1)	0	0	0	0
P. aeruginosa (MIC: 2)-Favorable (n=1, 0, 0, 1)	1	0	0	1
P. aeruginosa (MIC: 4)-Favorable (n=0, 0, 3, 2)	0	0	1	1

P. aeruginosa (MIC: 8)-Favorable (n=0, 0, 0, 2)	0	0	0	2
P. aeruginosa (MIC: 16)-Favorable (n=0, 1, 0, 1)	0	1	0	0
P. aeruginosa (MIC: 32)-Favorable (n=0, 0, 1, 3)	0	0	1	3
P. aeruginosa (MIC: >32)-Favorable (n=0,0,1,4)	0	0	1	4

Statistical analyses

No statistical analyses for this end point

Secondary: The reason for treatment change/discontinuation in mMITT analysis set

End point title	The reason for treatment change/discontinuation in mMITT analysis set

End point description:

Proportion of patients in the mMITT analysis set for whom the assigned study treatment was changed, discontinued, or interrupted.

End point type	Secondary

End point timeframe:

From first infusion to last infusion of study therapy

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
Treatment Change	1	0	8	11
Treatment Change - Crcl change	1	0	5	10
Treatment Change - Other	0	0	3	1
Treatment discontinuation	4	0	3	1
Treatment discontinuation - AE	1	0	1	1
Treatment discontinuation - Other	3	0	2	0
Treatment interrupted	0	0	0	1
Treatment interrupted - Change of infusion site	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: The 28 days all cause mortality rate in mMITT analysis set

End point title	The 28 days all cause mortality rate in mMITT analysis set

End point description:

Proportion of patients with Day 28 all-cause mortality in mMITT analysis set. The death in the cIAI

patient were reviewed independently by the SRP Chair.

End point type	Secondary

End point timeframe:

From first infusion to Day 28

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	137	144
Units: Participant				
All cause mortality	1	0	3	3
Deaths due to disease progression	0	0	0	0
Number of patients with any AE with outcome=death	1	0	3	3

Statistical analyses

No statistical analyses for this end point

Secondary: The 28 days all cause mortality rate in EME at TOC analysis set

End point title	The 28 days all cause mortality rate in EME at TOC analysis set

End point description:

Proportion of patients with Day 28 all-cause mortality in EME at TOC analysis set. The death in the cIAI patient were reviewed independently by the SRP Chair.

End point type	Secondary

End point timeframe:

From first infusion to Day 28

End point values	cIAI:Best Available Therapy	cIAI:CAZ-AVI + metronidazole	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	8	124	131
Units: Participant				
All cause mortality	0	0	1	1
Deaths due to disease progression	0	0	0	0
Number of patients with any AE withoutcome=death	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations for ceftazidime (CAZ) within 15 minutes before/ after dose in PK analysis set

End point title	Plasma concentrations for ceftazidime (CAZ) within 15 minutes before/ after dose in PK analysis set[16]

End point description:

Blood samples were taken at anytime within 15 minutes prior to or after stopping study drug on Day 3 for ceftazidime and avibactam plasma concentration.

End point type	Secondary

End point timeframe:

Anytime within 15 minutes prior to or after stopping study drug

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No treatment comparisons were done in this study. No no statistical analysis section were entered.

End point values	cIAI:CAZ-AVI + metronidazole	cUTI:CAZ-AVI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	145		
Units: NG/ML				
geometric mean (full range (min-max))	23880.3 (2700 to 80900)	74260.2 (5970 to 1640000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations for avibactam (AVI) within 15 minutes before/ after study dose in PK analysis set

End point title	Plasma concentrations for avibactam (AVI) within 15 minutes before/ after study dose in PK analysis set[17]

End point description:

Blood samples were taken at anytime within 15 minutes prior to or after stopping study drug on Day 3 for ceftazidime and avibactam plasma concentration.

End point type	Secondary

End point timeframe:

Anytime within 15 minutes prior to or after stopping study drug

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No treatment comparisons were done in this study. No no statistical analysis section were entered.

End point values	cIAI:CAZ-AVI + metronidazole	cUTI:CAZ-AVI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	147		
Units: NG/ML				
geometric mean (full range (min-max))	3061.3 (286 to 13200)	10103.8 (504 to 376000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations for ceftazidime (CAZ) between 30 to 90 minutes after dose in PK analysis set

End point title	Plasma concentrations for ceftazidime (CAZ) between 30 to 90 minutes after dose in PK analysis set[18]

End point description:

Blood samples were taken at anytime between 30 to 90 minutes after stopping study drug on Day 3 for ceftazidime and avibactam plasma concentration.

End point type	Secondary

End point timeframe:

anytime between 30 to 90 minutes after stopping study drug

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No treatment comparisons were done in this study. No no statistical analysis section were entered.

End point values	cIAI:CAZ-AVI + metronidazole	cUTI:CAZ-AVI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	141		
Units: NG/ML				
geometric mean (full range (min-max))	39465.3 (2620 to 85500)	56905.9 (14700 to 1910000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations for avibactam (AVI) between 30 to 90 minutes after dose in PK analysis set

End point title	Plasma concentrations for avibactam (AVI) between 30 to 90 minutes after dose in PK analysis set[19]

End point description:

Blood samples were taken at anytime between 30 to 90 minutes after stopping study drug on Day 3 for ceftazidime and avibactam plasma concentration.

End point type	Secondary

End point timeframe:

anytime between 30 to 90 minutes after stopping study drug

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No treatment comparisons were done in this study. No no statistical analysis section were entered.

End point values	cIAI:CAZ-AVI + metronidazole	cUTI:CAZ-AVI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	147		
Units: NG/ML				
geometric mean (full range (min-max))	6304.1 (285 to 15500)	8141.2 (773 to 405000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations for ceftazidime (CAZ) between 300 to 360 minutes after dose in PK analysis set

End point title	Plasma concentrations for ceftazidime (CAZ) between 300 to 360 minutes after dose in PK analysis set[20]

End point description:

Blood samples were taken at anytime between 300 to 360 minutes after stopping study drug on Day 3 for ceftazidime and avibactam plasma concentration.

End point type	Secondary

End point timeframe:

anytime between 300 to 360 minutes after stopping study drug

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No treatment comparisons were done in this study. No no statistical analysis section were entered.

End point values	cIAI:CAZ-AVI + metronidazole	cUTI:CAZ-AVI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	146		
Units: NG/ML				
geometric mean (full range (min-max))	14904.8 (2500 to 58100)	21442 (2490 to 1600000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations for avibactam (AVI) between 300 to 360 minutes after dose in PK analysis set

End point title	Plasma concentrations for avibactam (AVI) between 300 to 360 minutes after dose in PK analysis set[21]

End point description:

Blood samples were taken at anytime between 300 to 360 minutes after stopping study drug on Day 3 for ceftazidime and avibactam plasma concentration.

End point type	Secondary

End point timeframe:

anytime between 300 to 360 minutes after stopping study drug

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No treatment comparisons were done in this study. No no statistical analysis section were entered.

End point values	cIAI:CAZ-AVI + metronidazole	cUTI:CAZ-AVI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	146		
Units: NG/ML				
geometric mean (full range (min-max))	1769.3 (277 to 7900)	2425 (315 to 431000)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Non serious AEs and SAEs were from the first infusion of study therapy through the FU visits (cIAI: 28-35 days calendar days from randomization, cUTI: 28-32 calendar days from randomization).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	cIAI:Best Available Therapy
Reporting group description: cIAI: Best Available Therapy Determinated by Investigator	
Reporting group title	cUTI:Best Available Therapy
Reporting group description: cUTI:Best Available Therapy Determinated by Investigator	
Reporting group title	cUTI:CAZ-AVI
Reporting group description: cUTI: CAZ-AVI (2000 mg ceftazidime/500 mg avibactam)	
Reporting group title	cIAI:CAZ-AVI + metronidazole
Reporting group description: cIAI:CAZ-AVI (2000 mg ceftazidime/500 mg avibactam) plus metronidazole (500 mg)	

Serious adverse events	cIAI:Best Available Therapy	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)	5 / 153 (3.27%)	7 / 152 (4.61%)
number of deaths (all causes)	1	3	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pancreatic injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural fistula			

subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 15 (0.00%)	2 / 153 (1.31%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernial eventration			

subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	cIAI:CAZ-AVI + metronidazole		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Pancreatic injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural fistula			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			

subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hernial eventration				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Renal failure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lobar pneumonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	cIAI:Best Available Therapy	cUTI:Best Available Therapy	cUTI:CAZ-AVI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 15 (80.00%)	36 / 153 (23.53%)	18 / 152 (11.84%)
Vascular disorders			

Phlebitis			
subjects affected / exposed	1 / 15 (6.67%)	2 / 153 (1.31%)	1 / 152 (0.66%)
occurrences (all)	2	2	1
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Hyperthermia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 153 (1.31%)	4 / 152 (2.63%)
occurrences (all)	0	3	8
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Pulmonary fibrosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Atelectasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Hydrothorax			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Tachypnoea			

subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	4 / 15 (26.67%)	0 / 153 (0.00%)	2 / 152 (1.32%)
occurrences (all)	4	0	2
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Endoscopy gastrointestinal abnormal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	1 / 15 (6.67%)	2 / 153 (1.31%)	0 / 152 (0.00%)
occurrences (all)	1	3	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Arrhythmia supraventricular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Cardiovascular insufficiency			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0

Palpitations			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Supraventricular tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Parosmia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	1 / 152 (0.66%)
occurrences (all)	0	1	1
Headache			
subjects affected / exposed	1 / 15 (6.67%)	11 / 153 (7.19%)	1 / 152 (0.66%)
occurrences (all)	1	17	1
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	4 / 153 (2.61%)	3 / 152 (1.97%)
occurrences (all)	4	5	3
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	2 / 152 (1.32%)
occurrences (all)	1	0	2

Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	8 / 153 (5.23%)	3 / 152 (1.97%)
occurrences (all)	0	8	4
Duodenitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 15 (0.00%)	5 / 153 (3.27%)	2 / 152 (1.32%)
occurrences (all)	0	5	2
Enteritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Pancreatitis acute			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences (all)	1	1	0
Gastritis erosive			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	9 / 153 (5.88%)	5 / 152 (3.29%)
occurrences (all)	1	9	5
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	2 / 153 (1.31%)	4 / 152 (2.63%)
occurrences (all)	1	2	5
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 15 (6.67%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences (all)	1	1	0
Hyperhidrosis			

subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	2 / 152 (1.32%)
occurrences (all)	0	1	2
Rash			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 153 (0.65%)	1 / 152 (0.66%)
occurrences (all)	1	1	1
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	2 / 152 (1.32%)
occurrences (all)	0	0	2
Neck pain			

subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Incision site infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Orchitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences (all)	0	1	0
Metabolic acidosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 15 (6.67%)	0 / 153 (0.00%)	1 / 152 (0.66%)
occurrences (all)	1	0	1

Non-serious adverse events	cIAI:CAZ-AVI + metronidazole		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)		
Vascular disorders			
Phlebitis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
General disorders and administration site conditions			
Catheter site haemorrhage			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperthermia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pulmonary fibrosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Atelectasis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hydrothorax			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tachypnoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			

Depression			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Endoscopy gastrointestinal abnormal			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Arrhythmia supraventricular			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cardiovascular insufficiency			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Supraventricular tachycardia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Nervous system disorders Hydrocephalus subjects affected / exposed occurrences (all) Parosmia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2 2 / 12 (16.67%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 2 / 12 (16.67%) 2		

Duodenitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1			
Dyspepsia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0			
Enteritis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1			
Oesophagitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0			
Pancreatitis acute subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1			
Gastritis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0			
Gastritis erosive subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1			
Nausea subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3			
Vomiting subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2			
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1			
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1			
Skin ulcer				

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Incision site infection subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Orchitis subjects affected / exposed occurrences (all) Respiratory tract infection viral subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Metabolic acidosis subjects affected / exposed occurrences (all) Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported