Clinical trial results:
A Phase III, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime-Avibactam (CAZ AVI) Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-Abdominal Infections (cIAIs) in Hospitalized Adults

Summary

EudraCT number	2011-003895-35
Trial protocol	DE BE CZ GR ES BG IT LT
Global end of trial date	07 April 2014

Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	D4280C00001/5

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Alderley Park, Macclesfield, United Kingdom, SK10 4TG
Public contact	Paul Newell, Medical Science Director, AstraZeneca, paul.newell@astrazeneca.com
Scientific contact	Paul Newell, Medical Science Director, AstraZeneca, paul.newell@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	01 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2014
Global end of trial reached?	Yes
Global end of trial date	07 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the noninferiority of CAZ AVI plus metronidazole compared to meropenem with respect to clinical cure at the TOC visit. For US FDA the primary objective was assessed in patients who have at least 1 identified pathogen (the microbiologically modified intent-to-treat (mMITT) analysis set). For the rest of world, the primary objective was assessed in patients in the modified-intent-to-treat (MITT) analysis set and in patients who are clinically evaluable (CE).

Protection of trial subjects:

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

Background therapy:

Patients in the CAZ-AVI treatment group also received Metronidazole. If Enterococcus species or MRSA was one of the pathogens suspected or isolated and, in the opinion of the investigator, specific therapy was indicated, then open-label vancomycin, linezolid, or daptomycin may have been added to either of the study regimens according to the usual practice of the investigator.

Evidence for comparator:

Patients in the comparator treatment group received Meropenem. If Enterococcus species or MRSA was one of the pathogens suspected or isolated and, in the opinion of the investigator, specific therapy was indicated, then open-label vancomycin, linezolid, or daptomycin may have been added to either of the study regimens according to the usual practice of the investigator.

Actual start date of recruitment	22 March 2012
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: 66
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czech Republic: 243
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	Lithuania: 7

Country: Number of subjects enrolled	Romania: 144
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 99
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	United States: 85
Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	India: 125
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Mexico: 20
Country: Number of subjects enrolled	Peru: 36
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Thailand: 21
Country: Number of subjects enrolled	Greece: 34
Worldwide total number of subjects	1066
EEA total number of subjects	569

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)	821
From 65 to 84 years	227
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 22 March 2012 and the last patient's last visit was 07 April 2014. Patients were adults who were hospitalised with complicated intra-abdominal infection (cIAI) that required surgery and IV antibiotics.

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CAZ-AVI + Metronidazole

Arm description:

CAZ (2000mg)/AVI (500mg): IV treatment

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

Dosage and administration details:

single vial filled with the sterile crystalline form of ceftazidime (2000 mg) and the sterile crystalline form of avibactam (500 mg)

Arm title	Meropenem

Arm description:

1000 mg: IV treatment

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

Dosage and administration details:
Meropenem powder for solution for infusion 1000 mg

Number of subjects in period 1	CAZ-AVI + Metronidazole	Meropenem
Started	532	534
Completed	474	494
Not completed	58	40
Consent withdrawn by subject	22	17
Adverse event, non-fatal	14	7
Not specified in study report	12	6
Condition improved/subject recovered	1	-
Lack of efficacy	7	8
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	CAZ-AVI + Metronidazole
Reporting group description: CAZ (2000mg)/AVI (500mg): IV treatment	
Reporting group title	Meropenem
Reporting group description: 1000 mg: IV treatment	

Reporting group values	CAZ-AVI + Metronidazole	Meropenem	Total
Number of subjects	532	534	1066
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)	411	410	821
From 65-84 years	115	112	227
85 years and over	6	12	18
Age Continuous | Units: Years			
arithmetic mean	49.8	50.3	
standard deviation	± 17.48	± 18.29	-
Gender, Male/Female Units: Participants			
Female	204	200	404
Male	328	334	662

End points

End points reporting groups

Reporting group title	CAZ-AVI + Metronidazole
Reporting group description: CAZ (2000mg)/AVI (500mg): IV treatment	
Reporting group title	Meropenem
Reporting group description: 1000 mg: IV treatment	

Primary: Clinical response at the Test of Cure (TOC) visit in the microbiologically Modified Intent-To-Treat (mMITT) analysis set (primary outcome for FDA).

End point title	Clinical response at the Test of Cure (TOC) visit in the microbiologically Modified Intent-To-Treat (mMITT) analysis set (primary outcome for FDA).
End point description: The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention is necessary.	
End point type	Primary
End point timeframe: TOC: 28 to 35 days after start of study drug	

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	410		
Units: Number of patients				
Clinical cure	337	349		
Clinical failure	37	30		
Indeterminate	39	31		

Statistical analyses

Statistical analysis title	Non-inferiority
Statistical analysis description: The primary objective of this study (FDA agreed) was to determine the noninferiority in the clinical cure rate for CAZ-AVI compared to that for Meropenem at TOC in the mMITT in adult subjects with cIAI.	
Comparison groups	CAZ-AVI + Metronidazole v Meropenem

Number of subjects included in analysis	823
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Risk difference (RD)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.64
upper limit	1.58

Notes:

[1] - Non-inferiority was determined by comparing the lower limit of the 95% confidence interval for risk difference (corresponding to a 97.5% 1-sided lower bound) to the non-inferiority marging of -12.5%

Primary: Clinical response at the TOC visit in the Modified Intent-To-Treat analysis set (co-primary outcome for Rest of World [ROW]).

End point title	Clinical response at the TOC visit in the Modified Intent-To-Treat analysis set (co-primary outcome for Rest of World [ROW]).

End point description:

The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

End point type	Primary

End point timeframe:

TOC: 28 to 35 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	520	523		
Units: Number of patients				
Clinical cure	429	444		
Clinical failure	47	39		
Indeterminate	44	40		

Statistical analyses

Statistical analysis title	Non-inferiority

Statistical analysis description:

The co-primary objective of this study (ROW agreed) was to determine the noninferiority in the clinical cure rate for CAZ-AVI compared to that for Meropenem at TOC in the MITT in adult subjects with cIAI.

Comparison groups	CAZ-AVI + Metronidazole v Meropenem

Number of subjects included in analysis	1043
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Risk difference (RD)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	2.1

Notes:

[2] - Non-inferiority was determined by comparing the lower limit of the 95% confidence interval for risk difference (corresponding to a 97.5% 1-sided lower bound) to the non-inferiority marging of -12.5%

Primary: Clinical response at the TOC visit in the Clinically Evaulable (CE) analysis set (co-primary outcome for Rest of World [ROW]).

End point title	Clinical response at the TOC visit in the Clinically Evaulable (CE) analysis set (co-primary outcome for Rest of World [ROW]).

End point description:

The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

End point type	Primary

End point timeframe:

TOC: 28 to 35 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	416		
Units: Number of patients				
Clinical cure	376	385		
Clinical failure	34	31		

Statistical analyses

Statistical analysis title	Non-inferiority

Statistical analysis description:

The co-primary objective of this study (ROW agreed) was to determine the noninferiority in the clinical cure rate for CAZ-AVI compared to that for Meropenem at TOC in the CE in adult subjects with cIAI.

Comparison groups	CAZ-AVI + Metronidazole v Meropenem
Number of subjects included in analysis	826
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Risk difference (RD)
Point estimate	-0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.61
upper limit	2.89

Notes:

[3] - Non-inferiority was determined by comparing the lower limit of the 95% confidence interval for risk difference (corresponding to a 97.5% 1-sided lower bound) to the non-inferiority marging of -12.5%

Secondary: Clinical cure at TOC in the microbiologically evaluable analysis set

End point title	Clinical cure at TOC in the microbiologically evaluable analysis set

End point description:

The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

End point type	Secondary

End point timeframe:

TOC: 28 to 35 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	265	287		
Units: Number of patients				
Clinical cure	244	272		
Clinical failure	21	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure at TOC in the extended microbiologically evaluable analysis set

End point title	Clinical cure at TOC in the extended microbiologically evaluable analysis set

End point description:

The proportion of patients meeting the cure criteria: complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

End point type	Secondary

End point timeframe:

TOC: 28 to 35 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	294		
Units: Number of patients				
Clinical cure	248	278		
Clinical failure	22	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response by visit in the primary population: microbiologically Modified Intent-to-Treat (mMITT) at EOT visit

End point title	Clinical response by visit in the primary population: microbiologically Modified Intent-to-Treat (mMITT) at EOT visit

End point description:

Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

End point type	Secondary

End point timeframe:

EOT: within 24 hours after last dose of study drug.

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	410		
Units: Number of patients				
Clinical cure	361	379		
Clinical failure	30	19		
Indeterminate	22	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response in the microbiologically Modified Intent- To-Treat analysis set at TOC visit

End point title	Per-patient microbiological response in the microbiologically Modified Intent- To-Treat analysis set at TOC visit

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 cases where the clinical response was changed to indeterminate due to an SRP 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:

TOC: 28 to 35 days after start of study drug.

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	410		
Units: Number of patients				
Favourable response	337	349		
Unfavourable response	37	31		
Indeterminate	39	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Favorable per-pathogen microbiological response for patients infected with ceftazidime-resistant pathogens in mMITT analysis set

End point title	Favorable per-pathogen microbiological response for patients infected with ceftazidime-resistant pathogens in mMITT analysis set

End point description:

The proportion of patients with a favorable per-pathogen microbiological response: favourable microbiological response includes: Eradication Absence of causative pathogen from specimens at the site of infection. Presumed eradication where, repeat cultures were not performed/clinically indicated in a patient who had a clinical response of cure.

End point type	Secondary

End point timeframe:

TOC: 28 to 35 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	64		
Units: Number of favourable responses				
Citrobacter freundii complex: n	1	2		
Citrobacter freundii complex: cure	1	2		
Enterobacter aerogenes: n	0	1		
Enterobacter aerogenes: cure	0	1		
Enterobacter cloacae: n	3	7		
Enterobacter cloacae: cure	2	7		
Escherichia coli: n	24	37		
Escherichia coli: cure	19	31		

Klebsiella pneumoniae: n	13	13		
Klebsiella pneumoniae: cure	10	9		
Morganella morganii: n	2	1		
Morganella morganii: cure	1	1		
Proteus mirabilis: n	2	3		
Proteus mirabilis: cure	2	3		
Serratia marcescens: n	1	0		
Serratia marcescens: cure	1	0		
Alcaligenes faecalis: n	1	2		
Alcaligenes faecalis: cure	1	2		
Comamonas testosteroni: n	1	0		
Comamonas testosteroni: cure	1	0		
Pseudomonas aeruginosa: n	2	4		
Pseudomonas aeruginosa: cure	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: The time to first defervescence in the clinically evaluable analysis set for patients who have fever at study entry

End point title	The time to first defervescence in the clinically evaluable analysis set for patients who have fever at study entry

End point description:

Time to first defervescence was calculated for patients with a fever (>38ºC) at baseline. Defervescence (≤37.8ºC) was defined as the absence of fever based on the highest temperature recorded on each study day. Time to first defervescence while on IV study therapy in the CE analysis set at TOC for patients who had fever at study entry is defined as time (in days) from the first dose of IV study therapy to first absence of fever.

End point type	Secondary

End point timeframe:

Test of Cure: 1 to 14 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	78		
Units: Number of patients				
Afebrile at time of last observation	84	72		
Censored at time of last observation	0	6		

Statistical analyses

Statistical analysis title	Time to first defervescence
Comparison groups	CAZ-AVI + Metronidazole v Meropenem

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.004
Method	Logrank

Secondary: Plasma concentrations for ceftazidime and avibactam

End point title	Plasma concentrations for ceftazidime and avibactam[4]

End point description:

Blood samples were taken from all patients on Day 3 for the pharmacokinetic evaluation of ceftazidime and avibactam plasma concentrations

End point type	Secondary

End point timeframe:

Anytime within 15 minutes prior to or after stopping study drug, anytime between 30 and 90 minutes after stopping study drug, anytime between 300 minutes and 360 minutes after stopping study drug

Notes:

[4] - 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: Data not avaliable.

End point values	CAZ-AVI + Metronidazole			
Subject group type	Reporting group			
Number of subjects analysed	499			
Units: Geometric means for CAZ and AVI concs				
geometric mean (full range (min-max))				
Ceftazidime: 30 mins before or after	50823 (171 to 3110000)			
Ceftazidime: 30-90 mins after	40053.1 (155 to 235000)			
Ceftazidime: 300-360 mins after	10967.6 (159 to 151000)			
Avibactam: 30 mins before or after	9229.4 (13 to 693000)			
Avibactam: 30-90 mins after	7163.9 (15 to 46800)			
Avibactam: 300-360 mins after	1690.7 (14 to 30800)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response by pathogen at TOC for patients infected with ceftazidime-resistant pathogens in microbiological modified intent to treat analysis set

End point title	Clinical response by pathogen at TOC for patients infected with ceftazidime-resistant pathogens in microbiological modified intent to treat analysis set

End point description:

Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

End point type	Secondary

End point timeframe:

Test of Cure: 28 to 35 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	64		
Units: Number of clinical cures				
All : n	47	64		
All : cure	39	55		
Citrobacter freundii complex : n	1	2		
Citrobacter freundii complex : cure	1	2		
Enterobacter aerogenes : n	0	1		
Enterobacter aerogenes: cure	0	1		
Enterobacter cloacae : n	3	7		
Enterobacter cloacae : cure	2	7		
Escherichia coli : n	24	37		
Escherichia coli : cure	19	31		
Klebsiella pneumoniae : n	13	13		
Klebsiella pneumoniae : cure	10	9		
Morganella morganii : n	2	1		
Morganella morganii : cure	1	1		
Proteus mirabilis : n	2	3		
Proteus mirabilis : cure	2	3		
Serratia marcescens : n	1	0		
Serratia marcescens : cure	1	0		
Alcaligenes faecalis : n	1	2		
Alcaligenes faecalis : cure	1	2		
Comamonas testosteroni : n	1	0		
Comamonas testosteroni : cure	1	0		
Pseudomonas aeruginosa : n	2	4		
Pseudomonas aeruginosa : cure	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Per-patient microbiological response at TOC for patients infected with ceftazidime-resistant pathogens in mMITT analysis set

End point title	Per-patient microbiological response at TOC for patients infected with ceftazidime-resistant pathogens in mMITT analysis set

End point description:

Microbiological 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 cases where the clinical response was changed to indeterminate due to an SRP 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:

Test of Cure: 28 to 35 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	64		
Units: Number of patients				
Favourable	39	55		
Unfavourable	7	1		
indeterminate	2	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical response by visit in the primary population: microbiologically Modified Intent-to-Treat (mMITT) at LFU visit

End point title	Clinical response by visit in the primary population: microbiologically Modified Intent-to-Treat (mMITT) at LFU visit

End point description:

Complete resolution or significant improvement of signs and symptoms of the index infection such that no further antibacterial therapy, drainage, or surgical intervention was necessary.

End point type	Secondary

End point timeframe:

LFU: 42 to 49 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	410		
Units: Number of patients				
Clinical Cure	340	347		
Clinical Failure	38	31		
Indeterminate	35	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Favourable per-pathogen microbiological response at TOC

End point title	Favourable per-pathogen microbiological response at TOC

End point description:

The number of patients meeting favourable microbiological response (eradication or presumed eradication). Pathogens identified in 30 or more patients at baseline are shown here.

End point type	Secondary

End point timeframe:

TOC: 28 to 35 days after start of study drug

End point values	CAZ-AVI + Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	410		
Units: Number of patients				
Escherichia coli: n	271	285		
Escherichia coli: cure	218	249		
Streptococcus anginosus group: n	72	61		
Streptococcus anginosus group: cure	59	50		
Klebsiella pneumoniae: n	51	49		
Klebsiella pneumoniae: cure	40	37		
Bacteroides fragilis: n	52	47		
Bacteroides fragilis: cure	45	38		
Pseudomonas aeruginosa: n	35	36		
Pseudomonas aeruginosa: cure	30	34		
Enterococcus faecalis: n	31	28		
Enterococcus faecalis: cure	22	23		
Bacteroides thetaiotaomicron: n	22	25		
Bacteroides thetaiotaomicron:: cure	18	21		
Bacteroides ovatus: n	22	20		
Bacteroides ovatus: cure	17	17		
Enterococcus faecium: n	16	22		
Enterococcus faecium: cure	13	18		
Klebsiella oxytoca: n	18	15		
Klebsiella oxytoca: cure	14	12		
Enterobacter cloacae: n	13	19		
Enterobacter cloacae: cure	11	16		
Staphylococcus aureus: n	18	14		
Staphylococcus aureus: cure	17	14		
Citrobacter freundii complex: n	18	12		
Citrobacter freundii complex: cure	14	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from screening/consent visit until late follow-up visit (Day -1/0 to Day 42). AE were summarised by number of patients. Number of occurrences were not summarised therefore number of patients are shown below.

Adverse event reporting additional description:

Number of occurrences were not reported in the CSR therefore number of patients shown here. Total number of patients with any AE are 233 vs 218. SAEs reported by >=2 patients in either group, or any SAE with outcome of death, are reported here (total patients with SAE 42 vs 40).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Meropenem

Reporting group description:

1000 mg: IV treatment

Reporting group title	CAZ-AVI + Metronidazole

Reporting group description:

CAZ (2000mg)/AVI (500mg): IV treatment.

Serious adverse events	Meropenem	CAZ-AVI + Metronidazole	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 529 (3.40%)	26 / 529 (4.91%)	
number of deaths (all causes)	5	8	
number of deaths resulting from adverse events	0	0	
Investigations			
Transaminases increased			
subjects affected / exposed	2 / 529 (0.38%)	0 / 529 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrointestinal stoma necrosis			
subjects affected / exposed	0 / 529 (0.00%)	2 / 529 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Shock			

subjects affected / exposed	0 / 529 (0.00%)	1 / 529 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Myocardial infarct			
subjects affected / exposed	2 / 529 (0.38%)	1 / 529 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 529 (0.19%)	2 / 529 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute myocardial infarction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 529 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 529 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravacular coagulation			
subjects affected / exposed	0 / 529 (0.00%)	1 / 529 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Sudden deat			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 529 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 529 (0.00%)	2 / 529 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 529 (0.57%)	3 / 529 (0.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	1 / 529 (0.19%)	3 / 529 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 529 (0.00%)	5 / 529 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	2 / 529 (0.38%)	0 / 529 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	0 / 529 (0.00%)	2 / 529 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopneumonia			
subjects affected / exposed	2 / 529 (0.38%)	2 / 529 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	2 / 529 (0.38%)	0 / 529 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Meropenem	CAZ-AVI + Metronidazole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	207 / 529 (39.13%)	239 / 529 (45.18%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 529 (4.54%)	15 / 529 (2.84%)	
occurrences (all)	24	15	
Hypotension			
subjects affected / exposed	12 / 529 (2.27%)	12 / 529 (2.27%)	
occurrences (all)	12	12	
Phlebitis			
subjects affected / exposed	11 / 529 (2.08%)	10 / 529 (1.89%)	
occurrences (all)	11	10	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 529 (1.70%)	15 / 529 (2.84%)	
occurrences (all)	9	15	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 529 (1.70%)	11 / 529 (2.08%)	
occurrences (all)	9	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 529 (2.27%)	10 / 529 (1.89%)	
occurrences (all)	12	10	
Pyrexia			
subjects affected / exposed	24 / 529 (4.54%)	24 / 529 (4.54%)	
occurrences (all)	24	24	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	17 / 529 (3.21%)	40 / 529 (7.56%)	
occurrences (all)	17	40	
Constipation			
subjects affected / exposed	20 / 529 (3.78%)	8 / 529 (1.51%)	
occurrences (all)	20	8	
Vomiting			
subjects affected / exposed	10 / 529 (1.89%)	24 / 529 (4.54%)	
occurrences (all)	10	24	
Nausea			
subjects affected / exposed	24 / 529 (4.54%)	36 / 529 (6.81%)	
occurrences (all)	24	36	
Abdominal distensio			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	11 / 529 (2.08%)	10 / 529 (1.89%)	
occurrences (all)	11	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 529 (2.46%)	11 / 529 (2.08%)	
occurrences (all)	13	11	
Infections and infestations			
Wound infection			
subjects affected / exposed	11 / 529 (2.08%)	13 / 529 (2.46%)	
occurrences (all)	11	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2011	Revised study plan to specify that additional ECGs are required in the event of a significant increase in QTcF (increase from baseline of ≥30 msec or QTcF >460 msec)
31 October 2011	Revised concomitant and poststudy treatments to provide additional information on the potential interactions between meropenem and/or metronidazole and oral anticoagulants. Added prothrombin time test to coagulation monitoring tests in order to calculate the international normalized ratio
16 July 2012	Removal of genetic and biomarker sampling from study design
16 July 2012	Revised to add the extended ME analysis set
16 July 2012	Revision of inclusion criteria with respect to female contraception
16 July 2012	Amended to allow enrollment of patients with open skin incisions (with fascial closure) for purposes of wound management, to clarify the timing of surgical wound examinations, and permit the use of negative pressure wound therapy.
16 July 2012	Amended to revise the volume of blood drawn from each patient for PK and blood culture sampling and remove the pharmacogenetic and biomarker blood samples
31 July 2012	Revised to allow the use of topical antibacterials and antifungals on sites other than the surgical site
31 July 2012	Revised to clarify the collection of blood for Coombs test and culture
31 July 2012	Revised to clarify follow-up procedures for patients who discontinued the study, or were enrolled in error/subsequently failed to meet entry criteria
29 July 2013	Revised to combine the 2 identical protocols, D4280C00001 and D4280C00005, into a single study database for all analyses
29 July 2013	Revised to clarify the structure and timing of visits and assessments
29 July 2013	Revised inclusion criteria for female contraception and pregnancy
29 July 2013	Amended to clarify that the IVRS system will be used to assign and enrollment code to the patients after consenting, but before eligibility is confirmed.
29 July 2013	Amended to clarify that the initial dosing must be based on the estimated CrCl value at baseline, whereas, dose changes due to fluctuations in CrCl values may be made at the investigator’s discretion
29 July 2013	Amended to clarify that the use of concomitant antibiotics should not be withheld if the patient requires additional antibiotic therapy as a safety measure
29 July 2013	Revision of the number of patients with perforated appendix and/or appendiceal abscess is increased to 40% of the study population

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This summary describes data collected from two identical CSPs (D4280C00005 and D4280C00005). With agreement from the EMA and the FDA the data have been combined into a single study database.

Notes: