Clinical trial results:
A single blind, randomised, multi-centre, active controlled, trial to evaluate safety, tolerability, pharmacokinetics and efficacy of ceftazidime and avibactam when given in combination with metronidazole, compared with meropenem, in children from 3 months to less than 18 years of age with complicated intra-abdominal infections (cIAIs).

Summary

EudraCT number	2014-003242-28
Trial protocol	HU ES CZ GR RO
Global end of trial date	01 June 2017

Results information

Result version number	v1 (current)
This version publication date	13 December 2017
First version publication date	13 December 2017

Trial information

Trial identification

Sponsor protocol code	C3591004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02475733
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001313-PIP01-12
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of ceftazidime and avibactam (CAZ-AVI) plus metronidazole is given at the selected dose regimen versus meropenem in paediatric subjects aged greater than or equal to (>=)3 months to less than (<)18 years with cIAI

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 3
Worldwide total number of subjects	83
EEA total number of subjects	51

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)	1
Children (2-11 years)	52
Adolescents (12-17 years)	30
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 83 subjects were enrolled in multiple sites in 10 countries. Study started from 01-Aug-2015 and completed on 01-Jun-2017.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Ceftazidime- Avibactam (CAZ-AVI) plus Metronidazole

Arm description:

Subjects with Creatinine clearance(CrCL) >=50 milliliter per minute (mL/min) received 10 milligram per kilogram (mg/kg) intravenous(IV) infusion of metronidazole over 20 to 30 minutes along with 2 hour IV infusion of CAZ/AVI in following manner: 1)Age 6 to less than(<)18 years: 2000 mg CAZ/500 mg AVI (body weight >=40 kg), 50 mg/kg CAZ/12.5 mg/kg AVI (body weight <40 kg), 2) Age 6 months to <6 years: 50 mg/kg CAZ/12.5 mg/kg AVI, 3)Age 3 months to <6 months: 40 mg/kg CAZ/10 mg/kg AVI. Both infusions were administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days. Dose of CAZ-AVI was reduced to 50% if CrCl of subject decreased to <=50mL/min, and subject was removed from study therapy, if CrCl decreased below 30mL/min. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Ceftazidime- Avibactam (CAZ-AVI) plus Metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with Creatinine clearance(CrCL) >=50 milliliter per minute (mL/min) received 10 milligram per kilogram (mg/kg) intravenous(IV) infusion of metronidazole over 20 to 30 minutes along with 2 hour IV infusion of CAZ/AVI in following manner: 1)Age 6 to less than(<)18 years: 2000 mg CAZ/500 mg AVI (body weight >=40 kg), 50 mg/kg CAZ/12.5 mg/kg AVI (body weight <40 kg), 2) Age 6 months to <6 years: 50 mg/kg CAZ/12.5 mg/kg AVI, 3)Age 3 months to <6 months: 40 mg/kg CAZ/10 mg/kg AVI. Both infusions were administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days.

Arm title	Meropenem

Arm description:

Subjects received 15 to 30 minutes IV infusion of meropenem 20 mg/kg every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at the investigator's discretion.

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

Dosage and administration details:

Subjects received 15 to 30 minutes IV infusion of meropenem 20 mg/kg every 8 hours for a minimum of 72 hours and up to a
maximum duration of 15 days. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at the investigator's discretion.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The assessor was kept blinded in this study to remove any bias during clinical assessments related to safety and efficacy

Number of subjects in period 1	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem
Started	61	22
Completed	59	22
Not completed	2	0
Physician decision	1	-
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Ceftazidime- Avibactam (CAZ-AVI) plus Metronidazole

Reporting group description:

Subjects with Creatinine clearance(CrCL) >=50 milliliter per minute (mL/min) received 10 milligram per kilogram (mg/kg) intravenous(IV) infusion of metronidazole over 20 to 30 minutes along with 2 hour IV infusion of CAZ/AVI in following manner: 1)Age 6 to less than(<)18 years: 2000 mg CAZ/500 mg AVI (body weight >=40 kg), 50 mg/kg CAZ/12.5 mg/kg AVI (body weight <40 kg), 2) Age 6 months to <6 years: 50 mg/kg CAZ/12.5 mg/kg AVI, 3)Age 3 months to <6 months: 40 mg/kg CAZ/10 mg/kg AVI. Both infusions were administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days. Dose of CAZ-AVI was reduced to 50% if CrCl of subject decreased to <=50mL/min, and subject was removed from study therapy, if CrCl decreased below 30mL/min. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at investigator's discretion.

Reporting group title	Meropenem

Reporting group description:

Subjects received 15 to 30 minutes IV infusion of meropenem 20 mg/kg every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at the investigator's discretion.

Reporting group values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem	Total
Number of subjects	61	22	83
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	1	1
Children (2-11 years)	39	13	52
Adolescents (12-17 years)	22	8	30
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	10.4	9.7	
standard deviation	± 3.64	± 3.97	-
Gender, Male/Female Units: Subjects			
Female	17	13	30
Male	44	9	53
Race/Ethnicity, Customized Units: Subjects			
White	53	16	69
Asian	7	4	11
American Indian or Alaska Native	1	0	1
Other	0	2	2

End points

End points reporting groups

Reporting group title	Ceftazidime- Avibactam (CAZ-AVI) plus Metronidazole

Reporting group description:

Subjects with Creatinine clearance(CrCL) >=50 milliliter per minute (mL/min) received 10 milligram per kilogram (mg/kg) intravenous(IV) infusion of metronidazole over 20 to 30 minutes along with 2 hour IV infusion of CAZ/AVI in following manner: 1)Age 6 to less than(<)18 years: 2000 mg CAZ/500 mg AVI (body weight >=40 kg), 50 mg/kg CAZ/12.5 mg/kg AVI (body weight <40 kg), 2) Age 6 months to <6 years: 50 mg/kg CAZ/12.5 mg/kg AVI, 3)Age 3 months to <6 months: 40 mg/kg CAZ/10 mg/kg AVI. Both infusions were administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days. Dose of CAZ-AVI was reduced to 50% if CrCl of subject decreased to <=50mL/min, and subject was removed from study therapy, if CrCl decreased below 30mL/min. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at investigator's discretion.

Reporting group title	Meropenem

Reporting group description:

Subjects received 15 to 30 minutes IV infusion of meropenem 20 mg/kg every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at the investigator's discretion.

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to late follow-up (LFU) visit (Within 20 to 35 days after last dose of any study drug [IV or oral]) that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAE and non-SAE. Safety analysis set included all randomized subjects who received any amount of IV study medication.

End point type	Primary

End point timeframe:

From signature of informed consent until the LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days)

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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (not applicable)				
AEs	52.5	59.1		
SAEs	8.2	4.5		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Cephalosporin Class Effects and Additional AEs of Special Interest (AEoSI)

End point title	Percentage of Subjects With Cephalosporin Class Effects and Additional AEs of Special Interest (AEoSI)[2]

End point description:

Percentage of subjects with Cephalosporin class effects (defined as AeoSI within the safety topics (ST) of hypersensitivity/anaphylaxis, diarrhea, renal disorder and liver disorder) and additional AEs (which included AEs with preferred terms[PT] in the MedDRA 20.0 system organ class [SOC] of nervous system disorders and other AEs of clinical importance [such as seizures] relevant to the cephalosporin class) were reported in this outcome measure. LFU visit occurred within 27 to 50 days after start of study treatment (IV or oral).

End point type	Primary

End point timeframe:

From signature of informed consent until the LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days)

Notes:

[2] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (not applicable)				
AEoSI in the ST of Diarrhea	1.6	0		
AEoSI in the ST of Hypersensitivity/Anaphylaxis	4.9	13.6		
AEoSI in the ST of Liver Disorder	0	0		
AEoSI in the ST of Renal Disorder	0	0		
AEs with PTs in the Nervous System Disorder SOC	1.6	4.5		
AE of seizure	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Pulse Rate at End of Intravenous Therapy (EOIV) Visit

End point title	Change From Baseline in Pulse Rate at End of Intravenous Therapy (EOIV) Visit[3]

End point description:

EOIV visit occurred within 24 hours after completion of last infusion of the study drug. Safety analysis set included all randomized subjects who received any amount of IV study medication. Here, 'n' signifies those subjects who were evaluable at specified time points, for each arm respectively.

End point type	Primary

End point timeframe:

Baseline, EOIV visit (Day 4 up to 16)

Notes:

[3] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: beats per minute				
arithmetic mean (standard deviation)				
Baseline (n= 61, 22)	102.1 (± 17.07)	103.0 (± 23.31)		
Change at EOIV (n= 60, 22)	-15.2 (± 20.45)	-15.4 (± 21.74)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at End of Intravenous Therapy (EOIV) Visit

End point title	Change From Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at End of Intravenous Therapy (EOIV) Visit[4]

End point description:

EOIV visit occurred within 24 hours after completion of last infusion of the study drug. Safety analysis set included all randomized subjects who received any amount of IV study medication. Here, 'n' signifies those subjects who were evaluable at specified time points, for each arm respectively.

End point type	Primary

End point timeframe:

Baseline, EOIV visit (Day 4 up to 16)

Notes:

[4] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP: Baseline (n= 60, 22)	109.7 (± 13.90)	111.6 (± 13.06)		
SBP: Change at EOIV (n= 59, 22)	-4.0 (± 12.32)	-6.0 (± 13.66)		
DBP: Baseline (n= 60, 22)	63.5 (± 10.36)	63.1 (± 13.51)		
DBP: Change at EOIV (n= 59, 22)	1.3 (± 11.99)	-2.8 (± 14.14)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Respiratory Rate at End of Intravenous Therapy (EOIV) Visit

End point title	Change From Baseline in Respiratory Rate at End of Intravenous Therapy (EOIV) Visit[5]

End point description:

EOIV visit occurred within 24 hours after completion of last infusion of the study drug. Safety analysis set included all randomized subjects who received any amount of IV study medication. Here, 'n' signifies those subjects who were evaluable at specified time points, for each arm respectively.

End point type	Primary

End point timeframe:

Baseline, EOIV visit (Day 4 up to 16)

Notes:

[5] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: breaths per minute				
arithmetic mean (standard deviation)				
Baseline (n= 58, 21)	22.4 (± 5.02)	22.9 (± 5.79)		
Change at EOIV (n= 56, 21)	-1.3 (± 4.57)	-1.3 (± 4.44)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Body Weight at End of Intravenous Therapy

(EOIV) Visit

End point title	Change From Baseline in Body Weight at End of Intravenous Therapy (EOIV) Visit[6]

End point description:

EOIV visit occurred within 24 hours after completion of last infusion of the study drug. Safety analysis set included all randomized subjects who received any amount of IV study medication. Here, 'n' signifies those subjects who were evaluable at specified time points, for each arm respectively.

End point type	Primary

End point timeframe:

Baseline, EOIV visit (Day 4 up to 16)

Notes:

[6] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: kilograms				
arithmetic mean (standard deviation)				
Baseline (n= 61, 22)	40.58 (± 16.286)	38.35 (± 16.685)		
Change at EOIV (n= 56, 20)	-0.38 (± 1.442)	-1.06 (± 1.490)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Body Temperature at End of Intravenous Therapy (EOIV) Visit

End point title	Change From Baseline in Body Temperature at End of Intravenous Therapy (EOIV) Visit[7]

End point description:

EOIV visit occurred within 24 hours after completion of last infusion of the study drug. Safety analysis set included all randomized subjects who received any amount of IV study medication. Here, 'n' signifies those subjects who were evaluable at specified time points, for each arm respectively.

End point type	Primary

End point timeframe:

Baseline, EOIV visit (Day 4 up to 16)

Notes:

[7] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: degree Celsius				
arithmetic mean (standard deviation)				
Baseline (n= 60, 22)	37.35 (± 1.035)	37.16 (± 0.914)		
Change at EOIV (n= 59, 22)	-0.78 (± 0.987)	-0.60 (± 0.780)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Abnormal Physical Examination Findings at End of Intravenous Therapy (EOIV) Visit

End point title	Percentage of Subjects With Abnormal Physical Examination Findings at End of Intravenous Therapy (EOIV) Visit[8]

End point description:

Physical examination included an assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, respiratory system, cardiovascular system, abdomen, musculoskeletal system (including spine and extremities), and neurological system. Subjects with new or aggravated abnormal physical examination findings with regard to baseline findings were reported. Abnormality in physical examinations were based on blinded observer's discretion. EOIV visit occurred within 24 hours after completion of last infusion of the study drug. Safety analysis set included all randomized subjects who received any amount of IV study medication.

End point type	Primary

End point timeframe:

EOIV visit (Day 4 up to 16)

Notes:

[8] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: subjects of subjects				
number (not applicable)				
Abdomen	6.6	18.2		
Cardiovascular System	0	0		
General Appearance	1.6	0		
Head and Neck	0	0		
Lymph Nodes	0	0		
Musculoskeletal System	0	0		
Neurological System	0	0		
Respiratory System	3.3	0		
Skin	1.6	0		

Thyroid	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Abnormalities in Laboratory Parameters According to Potentially Clinically Significant Criteria

End point title	Percentage of Subjects With Abnormalities in Laboratory Parameters According to Potentially Clinically Significant Criteria[9]

End point description:

Criteria for potentially clinically significant laboratory abnormalities: Chemistry (calcium: <0.7*lower limit of normal range [LLN] and >30 percent decrease from baseline [DFB]; alanine aminotransferase [ALT]: >3*upper limit of normal range [ULN] and >300 percent IFB; alanine aminotransferase [AST]: >3*ULN and >300 percent IFB) and hematology (platelets: >2*ULN and >100 percent IFB). LFU visit occurred within 27 to 50 days after start of study treatment (IV or oral). Safety analysis set included all randomized subjects who received any amount of IV study medication. Here, 'n' signifies those subjects who were evaluable at specified time points, for each arm respectively.

End point type	Primary

End point timeframe:

From signature of informed consent until the LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days)

Notes:

[9] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (not applicable)				
Chemistry: Calcium (n= 53, 21)	1.9	0		
Chemistry: ALT (n= 59, 22)	1.7	0		
Chemistry: AST (n= 55, 21)	1.8	0		
Hematology: Platelets (n= 60, 22)	3.3	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Electrocardiogram (ECG) Parameter QTcF: > 450, >480 and >500 Millisecond (ms)

End point title	Percentage of Subjects With Electrocardiogram (ECG) Parameter QTcF: > 450, >480 and >500 Millisecond (ms)[10]

End point description:

ECG parameters included maximum QT intervals using Fridericia's correction (QTcF). Maximum QTcF >450 millisecond (ms); maximum QTcF >480 ms; and maximum QTcF >500 ms. LFU visit occurred within 27 to 50 days after start of study treatment (IV or oral). Safety analysis set included all randomized subjects who received any amount of IV study medication.

End point type	Primary

End point timeframe:

From signature of informed consent until the LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days)

Notes:

[10] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (not applicable)				
Maximum QTcF Interval : >450 ms	1.6	4.5		
Maximum QTcF Interval : >480 ms	1.6	4.5		
Maximum QTcF Interval : >500 ms	0	4.5		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Creatinine Clearance (CrCl) at Day 7

End point title	Percentage of Subjects With Creatinine Clearance (CrCl) at Day 7[11]

End point description:

CrCl is a measure of glomerular filtration rate (GMFR), an index of kidney function. It is the volume of blood plasma that is cleared of creatinine by the kidneys per unit time. Percentage of subjects with CrCl in the following categories were reported: <30 mL/min/1.73 m^2, >=30 to <50 mL/min/1.73 m^2, >=50 mL/min/1.73 m^2 to <80 mL/min/1.73 m^2, and >=80 mL/min/1.73 m^2. Safety analysis set included all randomized subjects who received any amount of IV study medication.

End point type	Primary

End point timeframe:

Day 7

Notes:

[11] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				

number (not applicable)				
CrCl: <30mL/min/1.73 m^2	0	0		
CrCl: >=30 to <50mL/min/1.73 m^2	0	0		
CrCl: >=50 to <80mL/min/1.73 m^2	0	0		
CrCl: >=80mL/min/1.73 m^2	50.8	59.1		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Creatinine Clearance (CrCl) at End of Intravenous Therapy (EOIV) Visit

End point title	Percentage of Subjects With Creatinine Clearance (CrCl) at End of Intravenous Therapy (EOIV) Visit[12]

End point description:

CrCl is a measure of GMFR, an index of kidney function. It is the volume of blood plasma that is cleared of creatinine by the kidneys per unit time. Percentage of subjects with CrCl in the following categories were reported: <30 mL/min/1.73 m^2, >=30 to <50 mL/min/1.73 m^2, >=50 mL/min/1.73 m^2 to <80 mL/min/1.73 m^2, and >=80 mL/min/1.73 m^2. EOIV visit occurred within 24 hours after completion of last infusion of the study drug. Safety analysis set included all randomized subjects who received any amount of IV study medication.

End point type	Primary

End point timeframe:

EOIV visit (Day 4 up to 16)

Notes:

[12] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (not applicable)				
CrCl: <30mL/min/1.73 m^2	0	0		
CrCl: >=30 to <50mL/min/1.73 m^2	0	0		
CrCl: >=50 to <80mL/min/1.73 m^2	0	0		
CrCl: >=80mL/min/1.73 m^2	82.0	81.8		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Creatinine Clearance (CrCl) at Test of Cure (TOC) Visit

End point title	Percentage of Subjects With Creatinine Clearance (CrCl) at Test of Cure (TOC) Visit[13]

End point description:

CrCl is a measure of GMFR, an index of kidney function. It is the volume of blood plasma that is cleared of creatinine by the kidneys per unit time. Percentage of subjects with CrCl in the following categories were reported: <30 mL/min/1.73 m^2, >=30 to <50 mL/min/1.73 m^2, >=50 mL/min/1.73 m^2 to <80 mL/min/1.73 m^2, and >=80 mL/min/1.73 m^2. TOC visit occurred within 8 to 15 days after last dose of any study drug (IV or oral). Safety analysis set included all randomized subjects who received any amount of IV study medication.

End point type	Primary

End point timeframe:

TOC is 8 to 15 days after last dose of IV or oral treatment (up to a maximum duration of 50 days)

Notes:

[13] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (not applicable)				
CrCl: <30mL/min/1.73 m^2	0	0		
CrCl: >=30 to <50mL/min/1.73 m^2	0	0		
CrCl: >=50 to <80mL/min/1.73 m^2	3.3	0		
CrCl: >=80mL/min/1.73 m^2	42.6	59.1		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Creatinine Clearance (CrCl) at Late Follow-up (LFU) Visit

End point title	Percentage of Subjects With Creatinine Clearance (CrCl) at Late Follow-up (LFU) Visit[14]

End point description:

CrCl is a measure of GMFR, an index of kidney function. It is the volume of blood plasma that is cleared of creatinine by the kidneys per unit time. Percentage of subjects with CrCl in the following categories were reported: <30 mL/min/1.73 m^2, >=30 to <50 mL/min/1.73 m^2, >=50 mL/min/1.73 m^2 to <80 mL/min/1.73 m^2, and >=80 mL/min/1.73 m^2. LFU visit occurred within 27 to 50 days after start of study treatment (IV or oral). Safety analysis set included all randomized subjects who received any amount of IV study medication.

End point type	Primary

End point timeframe:

LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days)

Notes:

[14] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (not applicable)				
CrCl: <30mL/min/1.73 m^2	0	0		
CrCl: >=30 to <50mL/min/1.73 m^2	0	0		
CrCl: >=50 to <80mL/min/1.73 m^2	1.6	0		
CrCl: >=80mL/min/1.73 m^2	6.6	9.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Ceftazidime and Avibactam

End point title	Plasma Concentrations of Ceftazidime and Avibactam[15]

End point description:

CAZ and AVI pharmacokinetic (PK) parameters derived from population PK analysis. This endpoint was not planned to be analyzed for meropenem receiving cohorts, as pre-specified in protocol. PK analysis set included all subjects who received at least 1 dose of study medication and had atleast 1 CAZ and/ or AVI plasma measurement available. Here, 'n' signifies those subjects who were evaluable at specified time points.

End point type	Secondary

End point timeframe:

15, 30-90, 300-360 minutes post-dose on Day 3

Notes:

[15] - 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 statistical analysis was planned for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: nanogram per milliliter				
geometric mean (standard deviation)				
Ceftazidime: 15 minute post-dose on Day 3(n= 59)	63565.5 (± 236761.80)			
Ceftazidime: 30-90 minute post-dose on Day 3(n=60)	38048.0 (± 19810.95)			
Ceftazidime:300-360minute post-dose on Day 3(n=60)	4603.0 (± 10308.96)			
Avibactam: 15 minute post-dose on Day 3(n=59)	12186.2 (± 55720.44)			
Avibactam: 30-90 minute post-dose on Day 3(n=60)	6548.6 (± 4437.55)			
Avibactam: 300-360 minute post-dose on Day 3(n=60)	821.5 (± 1968.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Clinical Response (CR) at End of 72 Hours Treatment: Intent-to-treat (ITT) Analysis Population

End point title	Percentage of Subjects With Favorable Clinical Response (CR) at End of 72 Hours Treatment: Intent-to-treat (ITT) Analysis Population

End point description:

Favorable CR was defined as resolution of all acute signs and symptoms of complicated intra- abdominal infection (cIAIs), or improvement to such an extent that no further antimicrobial therapy was required, or improvement but not enough to switch to oral therapy and still on IV study drug at end of 72 hours and had met following criterion: absence of new signs and symptoms, improvement in at least 1 symptom/sign (fever, pain, tenderness, elevated White Blood Cells [WBCs], elevated c-reactive protein) from baseline and no worsening symptom/sign. ITT analysis population included all subjects who had been assigned a randomized treatment.

End point type	Secondary

End point timeframe:

After 72 hours after the start of IV study infusion on Day 1

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (confidence interval 95%)	93.4 (85.2 to 97.7)	90.9 (73.9 to 98.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Clinical Response (CR) at End of Intravenous Therapy (EOIV) Visit: Intent-to-treat (ITT) Analysis Population

End point title	Percentage of Subjects With Favorable Clinical Response (CR) at End of Intravenous Therapy (EOIV) Visit: Intent-to-treat (ITT) Analysis Population

End point description:

Favorable CR was resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy was required, or improvement in subjects who had switch to oral therapy and met the following criterion: afebrile (temperature <=38.0°C) for at least 24 hours, absence of new and improvement in at least 1 symptom or sign (fever, pain, tenderness, elevated WBCs,

elevated c-reative-protein) from baseline and worsening of none. EOIV visit occurred within 24 hours after completion of last infusion of the study drug. ITT analysis population included all subjects who had been assigned a randomized treatment.

End point type	Secondary

End point timeframe:

EOIV visit (Day 4 up to 16)

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (confidence interval 95%)	96.7 (89.9 to 99.3)	100 (89.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Clinical Response (CR) at End of Treatment (EOT) Visit: Intent-to-treat (ITT) Analysis Population

End point title	Percentage of Subjects With Favorable Clinical Response (CR) at End of Treatment (EOT) Visit: Intent-to-treat (ITT) Analysis Population

End point description:

Favorable CR was resolution of all acute signs and symptoms of cIAI, or improvement to such an extent that no further antimicrobial therapy was required. EOT visit occurred within 48 hours after completion of the last dose of oral switch therapy or at time of premature discontinuation/early withdrawal from study if on oral switch therapy (which occurred within the maximum study treatment duration of 15 days). ITT analysis population included all subjects who had been assigned a randomized treatment.

End point type	Secondary

End point timeframe:

EOT visit (up to a maximum duration of Day 17 [48 hours after maximum study treatment of 15 days])

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (confidence interval 95%)	91.8 (83.0 to 96.8)	100 (89.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Clinical Response (CR) at Test of Cure (TOC) Visit: Intent-to-treat (ITT) Analysis Population

End point title	Percentage of Subjects With Favorable Clinical Response (CR) at Test of Cure (TOC) Visit: Intent-to-treat (ITT) Analysis Population

End point description:

Favorable CR was resolution of all acute signs and symptoms of cIAI, or improvement to such an extent that no further antimicrobial therapy was required. TOC visit occurred within 8 to 15 days after last dose of any study drug (IV or oral). ITT analysis population included all subjects who had been assigned a randomized treatment.

End point type	Secondary

End point timeframe:

TOC visit (8 to 15 days after last dose of IV or oral treatment; up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	22		
Units: percentage of subjects				
number (confidence interval 95%)	91.8 (83.0 to 96.8)	95.5 (80.7 to 99.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Clinical Response (CR): Clinically Evaluable (CE) Analysis Population

End point title	Percentage of Subjects With Favorable Clinical Response (CR): Clinically Evaluable (CE) Analysis Population

End point description:

Favorable CR: resolution of all acute signs, symptoms of cIAI, or improvement to such an extent that no further antimicrobial therapy required, or improvement in subjects who switch to oral therapy and met following criterion: afebrile (temperature<=38.0°C) for >=24 h, absence of new and improvement in at >= symptom or sign (fever, pain, tenderness, elevated WBCs, elevated c-reative-protein)from baseline and worsening of none. EOIV visit: 24 h after completion of last infusion of study drug. EOT visit occurred within 48 hours after completion of last dose of oral switch therapy or at time of premature discontinuation/early withdrawal from study if on oral switch therapy (which occurred within the maximum study treatment duration of 15 days). TOC visit: within 8 to 15 days after last dose of any study drug. CE analysis set. Here, 'n'= subjects evaluable at specified time points, for each arm respectively.

End point type	Secondary

End point timeframe:

After 72 hours after the start of IV study infusion on Day 1,EOIV(Day4 up to 16),EOT visit(up to a maximum duration of Day17[48h after maximum study treatment of 15days]) and TOC visit(up to a maximum study duration of 50days)

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	20		
Units: percentage of subjects				
number (confidence interval 95%)				
At the end 72 hours study medication (n= 49, 20)	98.0 (90.9 to 99.8)	95.0 (78.9 to 99.5)		
EOIV (n= 54, 20)	98.1 (91.7 to 99.8)	100 (88.3 to 100)		
EOT (n= 52, 20)	94.2 (85.4 to 98.3)	100 (88.3 to 100)		
TOC (n= 56, 20)	92.9 (83.9 to 97.5)	95.0 (78.9 to 99.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Microbiological Response: Microbiological Intent-to-treat (Micro-ITT) Population

End point title	Percentage of Subjects With Favorable Microbiological Response: Microbiological Intent-to-treat (Micro-ITT) Population

End point description:

Favorable microbiological response was achieved when all baseline pathogens were eradicated or presumed eradicated based on investigator's discretion. EOIV visit occurred within 24 hours after completion of last infusion of the study drug. EOIV visit occurred within 24 hours after completion of last infusion of the study drug. TOC visit occurred within 8 to 15 days after last dose of any study drug (IV or oral). LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days). Micro-ITT analysis population included all randomized subjects who had a baseline pathogen known to cause cIAI.

End point type	Secondary

End point timeframe:

EOIV visit (Day 4 up to 16), EOT visit (up to a maximum duration of Day 17 [48 hours after maximum study treatment of 15 days]) and TOC visit (up to a maximum study duration of 50 days) and LFU visit

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	19		
Units: percentage of subjects				
number (not applicable)				
EOIV	96.0	100		

EOT	90.0	100		
TOC	90.0	94.7		
LFU	90.0	94.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favorable Microbiological Response: Microbiologically Evaluable (ME) Population

End point title	Percentage of Subjects With Favorable Microbiological Response: Microbiologically Evaluable (ME) Population

End point description:

Favorable microbiological response was achieved when all baseline pathogens were eradicated or presumed eradicated based on investigator's discretion.EOIV visit occurred within 24hours after completion of last infusion of the study drug.EOT visit occurred within 48hours after completion of last dose of oral switch therapy or at time of premature discontinuation/early withdrawal from study if on oral switch therapy (which occurred within the maximum study treatment duration of 15 days). TOC visit occurred within 8 to 15 days after last dose of any study drug (IV or oral). LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days). ME analysis population=randomized subjects with cIAI who received study medication for >=48h and clinical failure or clinical failure with treatment limiting AE and subjects with >=72h treatment and favorable microbiological response.'n'= subjects who were evaluable at specified time points, for each arm respectively.

End point type	Secondary

End point timeframe:

EOIV visit (Day 4 up to 16), EOT visit (up to a maximum duration of Day 17 [48 hours after maximum study treatment of 15 days]), TOC visit (up to a maximum study duration of 50 days) and LFU visit

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	15		
Units: percentage of subjects				
number (not applicable)				
EOIV (n= 40, 15)	97.5	100		
EOT (n= 36, 15)	91.7	100		
TOC (n= 40, 15)	90.0	93.3		
LFU (n= 37, 14)	89.2	92.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Relapse at Late Follow-up (LFU) Visit: Clinically Evaluable (CE) Population

End point title	Percentage of Subjects With Clinical Relapse at Late Follow-up (LFU) Visit: Clinically Evaluable (CE) Population

End point description:

A subject was said to have clinical relapse if met either 1 of the following criteria: reappearance or worsening of signs and symptoms of cIAI that required further antimicrobial therapy and/or surgery, or death after TOC in which cIAI was contributory. LFU visit occurred within 27 to 50 days after start of study treatment (IV or oral). CE analysis population included randomized subjects with cIAI who received study medication for >=48h and clinical failure or clinical failure with treatment limiting AE and subjects with >=72h treatment and favorable clinicial response. Here, number of subjects analyzed=subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	18		
Units: percentage of subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Clinical Relapse at Late Follow-up (LFU) Visit: Microbiologically Evaluable (ME) Population

End point title	Percentage of Subjects with Clinical Relapse at Late Follow-up (LFU) Visit: Microbiologically Evaluable (ME) Population

End point description:

A subject was said to have clinical relapse if me either 1 of the following criteria: reappearance or worsening of signs and symptoms of cIAI that required further antimicrobial therapy and/or surgery, or death after TOC in which cIAI was contributory. LFU visit occurred within 27 to 50 days after start of study treatment (IV or oral). ME analysis population included randomized subjects with cIAI who received study medication for >=48h and clinical failure or clinical failure with treatment-limiting AE and subjects with >=72h treatment and favorable microbiological response. Number of subjects analyzed= subjects who were evaluable for this measure.

End point type	Secondary

End point timeframe:

LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	14		
Units: percentage of subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Emergent Infections: Microbiological Intent-to-treat (Micro-ITT) Population

End point title	Percentage of Subjects With Emergent Infections: Microbiological Intent-to-treat (Micro-ITT) Population

End point description:

Emergent infections were categorized as super infections and new infections. Superinfection: An intra-abdominal culture identified pathogen other than a baseline pathogen during the course of active treatment with study therapy along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy. New infection: An intra-abdominal culture identified pathogen other than a baseline pathogen at any time after study treatment had finished along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy. Subjects with any (super infections or new infections) of the infections were reported. Subjects with any (super infections or new infections) of the infections were reported. Micro-ITT analysis population included all randomized subjects who had a baseline pathogen known to cause cIAI.

End point type	Secondary

End point timeframe:

Baseline up to 50 days

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	19		
Units: percentage of subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Emergent Infections at Test of Cure (TOC) Visit: Microbiologically Evaluable Population

End point title	Percentage of Subjects with Emergent Infections at Test of Cure (TOC) Visit: Microbiologically Evaluable Population

End point description:

Emergent Infections was an intra-abdominal culture identified pathogen other than a baseline pathogen during the course of active treatment with study therapy along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy, new infection was an intra-abdominal culture identified pathogen other than a baseline pathogen at any time after study treatment has finished along with worsening signs and symptoms of infection requiring alternative antimicrobial therapy. TOC visit occurred within 8 to 15 days after last dose of any study drug (IV or oral). ME analysis population

included randomized subjects with cIAI who received study medication for >=48h and clinical failure or clinical failure with treatment limiting AE,and subjects with >=72h treatment and favorable microbiological response.

End point type	Secondary

End point timeframe:

TOC visit (8 to 15 days after last dose of IV or oral treatment; up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	Meropenem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	15		
Units: percentage of subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent until the LFU visit (27 to 50 days after start of study treatment, up to a maximum study duration of 50 days).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Meropenem

Reporting group description:

Subjects received 15 to 30 minutes IV infusion of meropenem 20 mg/kg every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at the investigator's discretion.

Reporting group title	Ceftazidime- Avibactam (CAZ-AVI) plus Metronidazole

Reporting group description:

Subjects with CrCL >=50 mL/min received 2-hour IV infusion of 2000 mg CAZ/500 mg AVI (subjects with body weight >=40 kg) or 50 mg/kg CAZ/12.5 mg/kg AVI (subjects with body weight <40 kg), followed by 10 mg/kg metronidazole IV infusion over 20 to 30 minutes. Both infusions were administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 15 days. Dose of CAZ-AVI was reduced to 50 percent, if the CrCl of subject decreased to <=50 mL/min, and subject was removed from study therapy, if CrCl decreased below 30 mL/min. After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at the investigator's discretion.

Serious adverse events	Meropenem	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	5 / 61 (8.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Postoperative ileus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 22 (4.55%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 22 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 22 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral meatus stenosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Meropenem	Ceftazidime-Avibactam (CAZ-AVI) plus Metronidazole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)	14 / 61 (22.95%)	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 22 (9.09%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Infusion site phlebitis			
subjects affected / exposed	0 / 22 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 22 (9.09%)	0 / 61 (0.00%)	
occurrences (all)	2	0	

Vomiting subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	9 / 61 (14.75%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2017	Added ITT and Micro-ITT analysis sets to the analysis in line with Food and Drug Administration (FDA) feedback; Added description of oral medications table summary; Amended AEs of SI to summarize by topic; Amended approach for summarising laboratory abnormality criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported