Clinical trial results:
A Single Blind, Randomised, Multi-Centre, Active Controlled, Trial To Evaluate Safety, Tolerability, Pharmacokinetics And Efficacy Of Ceftazidime And Avibactam (CAZ-AVI) Compared With Cefepime In Children From 3 Months To Less Than 18 Years Of Age With Complicated Urinary Tract Infections (cUTIs).

Summary

EudraCT number	2014-003244-13
Trial protocol	HU CZ GR PL RO
Global end of trial date	15 September 2017

Results information

Result version number	v2 (current)
This version publication date	13 March 2019
First version publication date	28 March 2018
Version creation reason	• Correction of full data set Correct made to Basic Results

Trial information

Trial identification

Sponsor protocol code	D4280C00016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02497781
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	15 December 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 September 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 CAZ-AVI given at the selected dose regimen versus cefepime in pediatric patients aged greater than or equal to (>=) 3 months to less than (<) 18 years with cUTI.

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	24 September 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	Taiwan: 17
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Czech Republic: 31
Country: Number of subjects enrolled	Greece: 22
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Russian Federation: 3
Worldwide total number of subjects	97
EEA total number of subjects	69

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)	38

Children (2-11 years)	40
Adolescents (12-17 years)	19
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 97 subjects were enrolled in multiple sites in 9 countries. Study started from 24-Sep-2015 and completed on 15-Sep-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	Investigator[1]

Arms

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

Arm description:

Subjects with Creatinine clearance(CrCL) >=50 milliliter per minute (mL/min) received single IV infusion of CAZ/AVI for 2 hour 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. The infusions was administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 14 days. Dose of CAZ-AVI was reduced to 50 percent if CrCl of subject drops below to 50mL/min, and subject was removed from study therapy, if CrCl drops 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)
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 single IV infusion of CAZ/AVI for 2 hour 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. The infusions was administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 14 days. Dose of CAZ-AVI was reduced to 50 percent if CrCl of subject drops below to 50mL/min, and subject was removed from study therapy, if CrCl drops below 30mL/min.

Arm title	Cefepime

Arm description:

Subjects received intravenous (IV) infusion of cefepime, at a dose and frequency prescribed by investigator's (maximum dose of cefepime in any single infusion not exceed 2000 mg every 12 hours). After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at investigator's discretion.

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

Dosage and administration details:

Subjects received intravenous (IV) infusion of cefepime, at a dose and frequency prescribed by investigator's (maximum dose of cefepime in any single infusion not exceed 2000 mg every 12 hours).

Notes:

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

Justification: confirmation that roles blinded are correct

Number of subjects in period 1	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime
Started	68	29
Treated	67	28
Completed	64	26
Not completed	4	3
Lack of efficacy	-	1
Consent withdrawn by subject	2	-
Randomised but not treated	1	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Ceftazidime- Avibactam (CAZ-AVI)

Reporting group description:

Subjects with Creatinine clearance(CrCL) >=50 milliliter per minute (mL/min) received single IV infusion of CAZ/AVI for 2 hour 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. The infusions was administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 14 days. Dose of CAZ-AVI was reduced to 50 percent if CrCl of subject drops below to 50mL/min, and subject was removed from study therapy, if CrCl drops 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	Cefepime

Reporting group description:

Subjects received intravenous (IV) infusion of cefepime, at a dose and frequency prescribed by investigator's (maximum dose of cefepime in any single infusion not exceed 2000 mg every 12 hours). After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at investigator's discretion.

Reporting group values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime	Total
Number of subjects	68	29	97
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)	27	11	38
Children (2-11 years)	28	12	40
Adolescents (12-17 years)	13	6	19
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	6.08	6.19	
standard deviation	± 5.647	± 6.072	-
Sex: Female, Male Units: Subjects			
Female	57	22	79
Male	11	7	18
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	12	5	17
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	50	24	74

More than one race	0	0	0
Unknown or Not Reported	5	0	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	67	29	96
Unknown or Not Reported	0	0	0
Height Units: centimeters			
arithmetic mean	108.7	108.9	
standard deviation	± 34.40	± 37.16	-

End points

End points reporting groups

Reporting group title	Ceftazidime- Avibactam (CAZ-AVI)

Reporting group description:

Subjects with Creatinine clearance(CrCL) >=50 milliliter per minute (mL/min) received single IV infusion of CAZ/AVI for 2 hour 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. The infusions was administered to subjects every 8 hours for a minimum of 72 hours and up to a maximum duration of 14 days. Dose of CAZ-AVI was reduced to 50 percent if CrCl of subject drops below to 50mL/min, and subject was removed from study therapy, if CrCl drops 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	Cefepime

Reporting group description:

Subjects received intravenous (IV) infusion of cefepime, at a dose and frequency prescribed by investigator's (maximum dose of cefepime in any single infusion not exceed 2000 mg every 12 hours). After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at 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 endpoint 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 AEs were events between first dose of study drug and up to late follow-up (LFU) visit (20 to 36 days after last dose of study treatment [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 (CAZ-AVI or Cefepime).

End point type	Primary

End point timeframe:

Baseline until the LFU visit (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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
Units: percentage of subjects				
number (not applicable)				
AEs|	53.7	50.0		
SAEs|	11.9	7.1		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Cephalosporin Class Effects and Additional Adverse Events (AEs)

End point title	Percentage of Subjects With Cephalosporin Class Effects and Additional Adverse Events (AEs)[2]

End point description:

Percentage of subjects with Cephalosporin class effects (defined as adverse event of special interest (AEoSI) within the safety topics (ST) of hypersensitivity/anaphylaxis) and additional AEs (which included AEs of diarrhea, renal disorder, hematological disorder and liver disorder relevant to the cephalosporin class within the safety topics (ST) based on MedDRA 20.0) were reported in this endpoint. Safety analysis set included all randomized subjects who received any amount of IV study medication (CAZ-AVI or Cefepime).

End point type	Primary

End point timeframe:

Baseline until the LFU visit (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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
Units: percentage of subjects				
number (not applicable)				
AE in the ST of Diarrhea|	7.5	10.7		
AE in the ST of Hematological Disorders|	0	0		
AEoSI in the ST of Hypersensitivity/Anaphylaxis|	7.5	7.1		
AE in the ST of Liver Disorder|	1.5	0		
AE in the ST of Renal Disorder|	0	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Pulse Rate at End of Intravenous Treatment (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 (CAZ-AVI or Cefepime).

End point type	Primary

End point timeframe:

Baseline, EOIV visit (anytime from Day 4 to 15)

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
Units: beats per minute				
arithmetic mean (standard deviation)				
Baseline|	111.5 (± 23.97)	119.1 (± 27.08)		
Change at EOIV|	-11.9 (± 18.65)	-17.1 (± 24.58)		

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 Treatment (EOIV) Visit

End point title	Change From Baseline in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at End of Intravenous Treatment (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 (CAZ-AVI or Cefepime).

End point type	Primary

End point timeframe:

Baseline, EOIV visit (anytime from Day 4 to 15)

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP: Baseline|	105.6 (± 14.88)	111.9 (± 14.61)		
SBP: Change at EOIV|	-1.0 (± 15.11)	-5.4 (± 14.53)		

DBP: Baseline|	62.6 (± 12.68)	69.1 (± 9.28)		
DBP: Change at EOIV|	0.9 (± 15.41)	-5.0 (± 7.50)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Respiratory Rate at End of Intravenous Treatment (EOIV) Visit

End point title	Change from Baseline in Respiratory Rate at End of Intravenous Treatment (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 (CAZ-AVI or Cefepime).

End point type	Primary

End point timeframe:

Baseline, EOIV visit (anytime from Day 4 to 15)

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
Units: breaths per minute				
arithmetic mean (standard deviation)				
Baseline|	25.8 (± 5.96)	27.0 (± 8.46)		
Change at EOIV|	-2.5 (± 4.64)	-2.6 (± 7.96)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Body Temperature at End of Intravenous Treatment (EOIV) Visit

End point title	Change from Baseline in Body Temperature at End of Intravenous Treatment (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 (CAZ-AVI or Cefepime). Here, number of subjects analyzed (N) signifies those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, EOIV visit (anytime from Day 4 to 15)

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	28		
Units: degree Celsius				
arithmetic mean (standard deviation)				
Baseline|	37.67 (± 1.043)	37.49 (± 1.031)		
Change at EOIV|	-1.15 (± 1.096)	-0.90 (± 1.036)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With Abnormal Physical Examination Findings at End of Intravenous Treatment (EOIV) Visit[7]

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 (CAZ-AVI or Cefepime).

End point type	Primary

End point timeframe:

EOIV visit (anytime from Day 4 to 15)

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
Units: percentage of subjects				
number (not applicable)				
Abdomen	0	3.6		
Cardiovascular System	1.5	0		
General Appearance	0	0		
Head and Neck	1.5	3.6		
Lymph Nodes	0	3.6		

Musculoskeletal System	0	0		
Neurological System	0	0		
Respiratory System	3.0	0		
Skin	3.0	7.1		
Thyroid	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Body Weight at End of Intravenous Treatment (EOIV) Visit

End point title	Change From Baseline in Body Weight at End of Intravenous Treatment (EOIV) Visit[8]

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 (CAZ-AVI or Cefepime). 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 (anytime from Day 4 to 15)

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
Units: kilogram				
arithmetic mean (standard deviation)				
Baseline (n= 67, 28)	24.55 (± 19.361)	25.24 (± 21.527)		
Change at EOIV (n= 66, 28)	-0.08 (± 0.613)	0.14 (± 0.510)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Potentially Clinically Significant (PCS) Abnormalities in Laboratory Parameters

End point title	Percentage of Subjects With Potentially Clinically Significant (PCS) Abnormalities in Laboratory Parameters[9]

End point description:

PCS criteria:Haematology(hemoglobin;hematocrit<0.6*lower limit of normal[LLN],>1.3*upper limit of normal[ULN],>25%decrease from baseline[DFB],>30%increase from baseline[IFB];RBC<0.8*LLN,>1.3*ULN,>25%DFB,>30%IFB;WBC<0.5*LLN,>2*ULN,>60%DFB,>100%I

2*ULN,>70%DFB,>100%IFB;Lymphocytes<0.2*LLN,>2.2*ULN,>70%DFB,>100%IFB;Eosinophils>4*ULN,>400%IFB;Platelets<0.4*LLN,>2*ULN,>40%DFB,>100%IFB);Chemistry(alanine aminotransferase;aspartate aminotransferase>3*ULN,>300%IFB;albumin<0.6*LLN,>60%DFB;alkalinephosphatase<0.5*LLN,>3*ULN,>80%DFB,>300%IFB;Bicarbonate<0.7*LLN,>1.3*ULN,>50%DFB,>30%IFB;blood urea nitrogen>3*ULN,>300%IFB;Calcium<0.7*LLN,>1.3*ULN,>30%DFB,>30%IFB;Chloride<0.8*LLN,>1.2*ULN,>20%DFB,>20%IFB;Cr>2*ULN,>100%IFB;Direct bilirubin>2.5*ULN,>150%IFB;Glucose,non-fasting<0.6*LLN,>4*ULN,>40%DFB,>200%IFB;Potassium<0.8*LLN,>1.2*ULN,>15%DFB,>20%IFB;Sodium<0.85*LLN,>1.1*ULN,>10%DFB,>10%IFB;Total bilirubin>2.5*ULN,>300%IFB).Safety analysis

End point type	Primary

End point timeframe:

Baseline until the LFU visit (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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	26		
Units: percentage of subjects				
number (not applicable)	1.6	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Potentially Clinically Significant Abnormalities in Electrocardiogram (ECG) Parameters

End point title	Percentage of Subjects With Potentially Clinically Significant Abnormalities in Electrocardiogram (ECG) Parameters[10]

End point description:

PCS criteria for abnormal value of ECG parameters: QT interval >=450 milliseconds (msec); 480 msec; >=500 msec; Increase from baseline (IFB) of >=30 msec; >=60 msec and >90 msec; Decrease from baseline (DFB) of >=30 msec; >=60 msec and >90 msec. QT interval using Bazett's correction (QTcB): >=450 milliseconds (msec); 480 msec; >=500 msec; Increase from baseline (IFB) of >=30 msec; >=60 msec and >90 msec; DFB of >=30 msec; >=60 msec and >90 msec. QT interval using Fridericia's correction (QTcF): >=450 msec; 480 msec; >=500 msec; IFB of >=30 msec; >=60 msec and >90 msec; DFB of >=30 msec; >=60 msec and >90 msec. EOIV visit occurred within 24 hours after completion of last infusion of the study drug.

End point type	Primary

End point timeframe:

Baseline until the EOIV visit (anytime from Day 4 to 15)

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
Units: percentage of subjects				
number (not applicable)				
QT Interval : >450 msec|	0	0		
QT Interval : >480 msec|	0	0		
QT Interval : >500 msec|	0	0		
Maximum IFB QT Interval : > 30 msec|	19.4	14.3		
Maximum IFB QT Interval : > 60 msec|	7.5	3.6		
Maximum IFB QT Interval : >90 msec|	3.0	0		
Maximum DFB QT Interval : > 30 msec|	9.0	17.9		
Maximum DFB QT Interval : > 60 msec|	4.5	0		
Maximum DFB QT Interval : > 90 msec|	1.5	0		
QTcB Interval : >450 msec|	16.4	3.6		
QTcB Interval : >480 msec|	11.9	0		
QTcB Interval : >500 msec|	7.5	0		
Maximum IFB QTcB Interval : > 30 msec|	17.9	14.3		
Maximum IFB QTcB Interval : > 60 msec|	7.5	3.6		
Maximum IFB QTcB Interval : > 90 msec|	3.0	0		
Maximum DFB QTcB Interval : > 30 msec|	10.4	7.1		
Maximum DFB QTcB Interval : > 60 msec|	6.0	3.6		
Maximum DFB QTcB Interval : > 90 msec|	1.5	3.6		
QTcF Interval : >450 msec|	6.0	0		
QTcF Interval : >480 msec|	6.0	0		
QTcF Interval : >500 msec|	6.0	0		
Maximum IFB QTcF Interval : > 30 msec|	17.9	14.3		
Maximum IFB QTcF Interval : > 60 msec|	3.0	3.6		
Maximum IFB QTcF Interval : > 90 msec|	3.0	0		
Maximum DFB QTcF Interval : > 30 msec|	9.0	10.7		
Maximum DFB QTcF Interval : > 60 msec|	3.0	3.6		
Maximum DFB QTcF Interval : > 90 msec|	1.5	0		

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 participants with CrCl in the following criteria were reported: <30 mL/min/1.73 m^2, >=30 to <50 mL/min/1.73 m^2, >=50 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 (CAZ-AVI or Cefepime).

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
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	11.1	0		
CrCl: >=80mL/min/1.73 m^2	88.9	100		

Statistical analyses

No statistical analyses for this end point

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

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

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 participants with CrCl in the following criteria were reported: <30 mL/min/1.73 m^2, >=30 to <50 mL/min/1.73 m^2, >=50 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 (CAZ-AVI or Cefepime).

End point type	Primary

End point timeframe:

EOIV visit (anytime from Day 4 to 15)

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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
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	20.0	13.6		
CrCl: >=80mL/min/1.73 m^2	80.0	86.4		

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 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 participants with CrCl in the following criteria were reported: <30 mL/min/1.73 m^2, >=30 to <50 mL/min/1.73 m^2, >=50 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 (CAZ-AVI or Cefepime).

End point type	Primary

End point timeframe:

TOC visit (up to a maximum study 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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	28		
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	25.0	41.7		
CrCl: >=80mL/min/1.73 m^2	75.0	58.3		

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[14]

End point description:

PK analysis set included all randomized subjects who received any amount of CAZ-AVI and had at least 1 CAZ and/ or AVI plasma measurement available. This endpoint was not planned to be analyzed for Cefepime receiving cohort, as pre-specified in protocol. Here, 'n' signifies those subjects who were evaluable at specified time points respectively.

End point type	Secondary

End point timeframe:

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

Notes:

[14] - 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 performed for this endpoint

End point values	Ceftazidime-Avibactam (CAZ-AVI)			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: nanogram per milliliter				
geometric mean (standard deviation)				
Ceftazidime: 15 minute post-dose on Day 3 (n= 62)	61411.2 (± 39276.40)			
Ceftazidime: 30-90minute post-dose on Day 3(n=59)	47638.5 (± 31948.31)			
Ceftazidime:300-360minute post-dose on Day 3(n=62)	7285.7 (± 11396.88)			
Avibactam: 15 minute post-dose on Day 3 (n= 62)	9577.4 (± 6922.76)			
Avibactam: 30-90 minute post-dose on Day 3 (n= 59)	7046.4 (± 6060.75)			
Avibactam: 300-360minute post-dose on Day 3(n=62)	936.3 (± 1499.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favourable Clinical Response (CR): Intent-to-treat (ITT) Analysis Population

End point title	Percentage of Subjects With Favourable Clinical Response (CR): Intent-to-treat (ITT) Analysis Population

End point description:

Favorable CR was defined as a CR of improvement and cure(at end of 72 hours(hr) and EOIV) and a CR of cure (at EOT and TOC). Cure defined as: resolution of all acute signs/symptoms of cUTI/improvement to such an extent that no further antimicrobial therapy required. Improvement defined as: 1) at end of 72hr study drug treatment: improvement but not enough to switch to oral therapy and still on IV study drug at end of 72hr and meet following criterion: Absence of new signs and symptoms, and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline, and with no worsening of any symptom or sign.2) at EOIV: subjects who switched to oral therapy and had afebrile (temperature<=38.0°C) for >=24 hr; absence of new and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline and worsening of none. ITT analysis population= all subjects who had been assigned a randomized treatment.

End point type	Secondary

End point timeframe:

End of 72 hours study drug treatment, EOIV visit (anytime from Day 4 to 15), EOT visit (up to Day 16), TOC visit (up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	29		
Units: percentage of subjects				
number (confidence interval 95%)				
End of 72 hours	88.2 (79.0 to 94.3)	86.2 (70.5 to 95.2)		
EOIV|	91.2 (82.7 to 96.2)	89.7 (74.9 to 97.0)		
EOT|	88.2 (79.0 to 94.3)	89.7 (74.9 to 97.0)		
TOC|	86.8 (77.2 to 93.2)	82.8 (66.3 to 93.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favourable Clinical Response (CR): Microbiological ITT (Micro-ITT) Analysis Population

End point title	Percentage of Subjects With Favourable Clinical Response (CR): Microbiological ITT (Micro-ITT) Analysis Population

End point description:

Favorable CR was defined as a CR of improvement and cure(at end of 72hr and EOIV) and a CR of cure(at EOT and TOC).Cure is resolution of all acute signs/symptoms of cUTI/improvement to such an extent that no further antimicrobial therapy required. Improvement is: 1)at end of 72hr study drug treatment: improvement but not enough to switch to oral therapy and still on IV study drug at end of 72hr and meet following criterion: Absence of new signs/symptoms, and improvement in atleast 1 signs/symptoms(fever,pain,tenderness,elevated WBCs and CRP) from Baseline, and with no worsening of any signs/symptoms. 2)at EOIV:subjects who switched to oral therapy and had afebrile(temperature<=38.0°C) for >=24hr; absence of new and improvement in atleast 1 signs/symptoms from Baseline and worsening of none. Micro-ITT analysis population=all randomized subjects who had atleast 1gram(-ve) typical pathogen(in the urine) at baseline known to cause cUTI and no gram(+ve) pathogen(in the urine) at baseline.

End point type	Secondary

End point timeframe:

End of 72 hours study drug treatment, EOIV visit (anytime from Day 4 to 15), EOT visit (up to Day 16), TOC visit (up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	23		
Units: percentage of subjects				
number (confidence interval 95%)				
At the end 72 hours study medication|	90.7 (80.9 to 96.4)	95.7 (81.4 to 99.5)		
EOIV|	96.3 (88.6 to 99.2)	95.7 (81.4 to 99.5)		
EOT|	90.7 (80.9 to 96.4)	95.7 (81.4 to 99.5)		
TOC|	88.9 (78.5 to 95.2)	82.6 (63.8 to 93.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favourable Clinical Response (CR) at End of 72 Hours Treatment: Clinically Evaluable (CE) Analysis Set at 72 Hours

End point title	Percentage of Subjects With Favourable Clinical Response (CR) at End of 72 Hours Treatment: Clinically Evaluable (CE) Analysis Set at 72 Hours

End point description:

Favourable CR was defined as a CR of improvement and cure. Cure was defined as resolution of all acute signs and symptoms of complicated urinary tract infections (cUTIs) or improvement to such an extent that no further antimicrobial therapy was required. Clinical Improvement included all the subjects who had improvement but not enough to switch to oral therapy and were still on IV study drug at End of 72 hours and had meet the following criterion: absence of new signs and symptoms, and improvement in at least 1 symptom or sign (fever, pain, tenderness, elevated WBCs, elevated CRP) from baseline, and with no worsening of any symptom or sign. CE analysis set at 72hr: subjects who had at least 1 gram negative typical pathogen (in urine) at baseline known to cause cUTI, no gram positive pathogen (in urine) at baseline, confirmed diagnosis of cUTI, >=48hr of IV study drug, unless discontinued due to treatment-limiting AE, no important protocol deviations and no concomitant antibiotics.

End point type	Secondary

End point timeframe:

End of 72 hours study drug treatment on Day 1

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	21		
Units: percentage of subjects				
number (confidence interval 95%)	100 (94.8 to 100)	95.2 (79.8 to 99.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favourable Clinical Response (CR) at End of Intravenous Treatment (EOIV) Visit: Clinically Evaluable (CE) Analysis Set at EOIV

End point title	Percentage of Subjects With Favourable Clinical Response (CR) at End of Intravenous Treatment (EOIV) Visit: Clinically Evaluable (CE) Analysis Set at EOIV

End point description:

Favourable CR was defined as a CR of improvement and cure. Cure was defined as resolution of all acute signs and symptoms of cUTIs or improvement to such an extent that no further antimicrobial therapy was required. Clinical Improvement included all the subjects who had switched to oral therapy and had meet 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-reactive-protein) from baseline and worsening of none. EOIV visit occurred within 24hours after completion of last infusion of the study drug. CE analysis set at EOIV: subjects >=1 gram negative typical pathogen known to cause cUTI, no gram positive pathogen (in urine) at baseline, confirmed cUTI diagnosis, >=48hr of IV study drug, unless discontinued due to AE, no important protocol deviations, no concomitant antibiotic, had clinical response of cure, improvement or failure at EOIV.

End point type	Secondary

End point timeframe:

EOIV visit (anytime from Day 4 to 15)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	22		
Units: percentage of subjects				
number (confidence interval 95%)	98.1 (91.4 to 99.8)	95.5 (80.7 to 99.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favourable Clinical Response (CR) at End of Treatment (EOT) Visit: Clinically Evaluable (CE) Analysis Set at EOT

End point title	Percentage of Subjects With Favourable Clinical Response (CR) at End of Treatment (EOT) Visit: Clinically Evaluable (CE) Analysis Set at EOT

End point description:

Favourable clinical response was defined as a CR cure. Cure was defined as resolution of all acute signs and symptoms of complicated urinary tract infections (cUTIs) or improvement to such an extent that no further antimicrobial therapy was required. CE analysis set at EOT: subjects >=1 gram negative typical pathogen known to cause cUTI, no gram positive pathogen (in urine) at baseline, confirmed cUTI diagnosis, >=48hr of IV study drug, unless discontinued due to AE, no important protocol deviations, no concomitant antibiotic, had clinical response of cure, improvement or failure at EOT. CE analysis set at EOT: subjects >=1 gram negative typical pathogen known to cause cUTI, no gram positive pathogen (in urine) at baseline, confirmed cUTI diagnosis, >=48hr of IV study drug, unless discontinued due to AE, no important protocol deviations, no concomitant antibiotic, had clinical response of cure, improvement or failure at EOT.

End point type	Secondary

End point timeframe:

EOT visit (up to Day 16)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	19		
Units: percentage of subjects				
number (confidence interval 95%)	98.0 (90.9 to 99.8)	94.7 (77.9 to 99.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favourable Clinical Response (CR) at TOC: Clinically Evaluable (CE) Analysis Set at TOC

End point title	Percentage of Subjects With Favourable Clinical Response (CR) at TOC: Clinically Evaluable (CE) Analysis Set at TOC

End point description:

Favourable clinical response was defined as resolution of all acute signs/symptoms of cUTIs or improvement to such an extent that no further antimicrobial therapy was needed. Subjects who met the following criterion: Incomplete resolution or worsening of cUTI signs or symptoms or development of new signs or symptoms requiring alternative non-study antimicrobial therapy or death in which cUTI was contributory. TOC visit occurred within 8 to 15 days after last dose of any study drug (IV or oral). CE analysis set at TOC: subjects >=1 gram negative typical pathogen known to cause cUTI, no gram positive pathogen (in urine) at baseline, confirmed cUTI diagnosis, >=48hr of IV study drug, unless discontinued due to AE, no important protocol deviations, no concomitant antibiotic, had clinical response of cure, improvement or failure at TOC.

End point type	Secondary

End point timeframe:

TOC visit (up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	20		
Units: percentage of subjects				
number (confidence interval 95%)	93.9 (84.6 to 98.2)	85.0 (65.1 to 95.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Favourable Clinical Response (CR): Microbiologically Evaluable (ME) Analysis Population

End point title	Percentage of Subjects With Favourable Clinical Response (CR): Microbiologically Evaluable (ME) Analysis Population

End point description:

Favorable CR: CR of improvement/cure(end of 72 hr and EOIV) and CR of cure(EOT and TOC).Cure: resolution of all acute signs/symptoms of cUTI/improvement such that no further antimicrobial therapy required. Improvement: 1)at end of 72 hr treatment: improvement but not enough to switch to oral therapy and still on IV study drug and meet following criterion: absence of new signs/symptoms, improvement in at least 1 symptom/sign from Baseline with no worsening of any symptom/sign. 2) EOIV: subjects who switched to oral therapy, had afebrile (temperature<=38.0°C) for >=24 hr; absence of new/improvement in at least 1 symptom/sign. ME analysis set: subjects >=1gram –ve, no gram +ve pathogen at baseline, confirmed cUTI diagnosis, had >=48 hr IV study drug, unless discontinued due to AE, no important protocol deviation, concomitant antibiotic, >=1gram –ve typical UTI bacterial pathogen at Baseline susceptible to study drug and MR which was not indeterminate.'n'=subjects evaluable for each arm.

End point type	Secondary

End point timeframe:

EOIV visit (Day 4 to 15), EOT visit(up to Day 16, TOC visit (up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	16		
Units: percentage of subjects				
number (confidence interval 95%)				
EOIV (n= 35, 16)	100 (93.1 to 100)	100 (85.7 to 100)		
EOT (n= 39, 14)	100 (93.8 to 100)	100 (83.8 to 100)		
TOC (n= 41, 16)	92.7 (81.7 to 97.9)	87.5 (65.6 to 97.3)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Favourable microbiological response was achieved when all baseline pathogens were eradicated. EOIV visit occurred within 24 hours after completion of last infusion of the study drug. 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 14 days). Micro-ITT analysis subjects included all randomized subjects who had at least 1 gram negative typical pathogen (in the urine) at baseline known to cause cUTI and no gram cUTI and no gram positive pathogen (in the urine) at baseline.

End point type	Secondary

End point timeframe:

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	23		
Units: percentage of subjects				
number (not applicable)				
EOIV|	81.5	78.3		
EOT|	83.3	73.9		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Favourable microbiological response was achieved when all baseline pathogens were eradicated. EOIV visit occurred within 24 hours after completion of last infusion of the study drug. 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 14 days). ME analysis set: subjects >=1gram(-ve) and no gram(+ve) pathogen (in urine) at baseline, confirmed cUTI diagnosis, had >=48hr IV study drug, unless discontinued due to AE, no important protocol deviation, concomitant antibiotic, >=1gram(-ve) typical UTI bacterial pathogen at Baseline susceptible to study drug and MR which was not indeterminate. Here, 'n' signifies those subjects who were evaluable at specified time points, for each arm respectively.

End point type	Secondary

End point timeframe:

EOIV visit (Day 4 to 15), EOT visit (up to Day 16)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	16		
Units: percentage of subjects				
number (not applicable)				
EOIV (n= 35, 16)	97.1	100		
EOT (n= 39, 14)	97.4	100		

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) Analysis Set at LFU

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

End point description:

A subjects was said to have clinical relapse if met either 1 of the following criteria: reappearance or worsening of signs and symptoms of cUTI that required further antimicrobial therapy and/or surgery or death after TOC in which cUTI was contributory. LFU visit occurred within 27 to 50 days after start of study treatment (IV or oral). CE analysis set at LFU: subjects >=1gram negative typical pathogen known to cause cUTI, no gram positive pathogen (in urine) at baseline, confirmed cUTI diagnosis, >=48hr of IV study drug, unless discontinued due to AE, no important protocol deviations, no concomitant antibiotic,were evaluated for clinical response of sustained cure or relapse.

End point type	Secondary

End point timeframe:

LFU visit (anytime up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	15		
Units: percentage of subjects				
number (not applicable)	6.8	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) Analysis Set at LFU

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

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 cUTI that required further antimicrobial therapy and/or surgery, or death after TOC in which cUTI was contributory. LFU visit occurred within 27 to 50 days after start of study treatment (IV or oral). ME analysis set: subjects >=1gram(-ve) and no gram(+ve) pathogen (in urine) at baseline, confirmed cUTI diagnosis, had >=48hr IV study drug, unless discontinued due to AE, no important protocol deviation, concomitant antibiotic, >=1gram(-ve) typical UTI bacterial pathogen at Baseline susceptible to study drug and MR which was not indeterminate.

End point type	Secondary

End point timeframe:

LFU visit (anytime up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	9		
Units: percentage of subjects				
number (not applicable)	12.5	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-infection and new infections. Superinfection: A urine 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: A urine 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. Percentage of subjects with any (super infections or new infections) of the infections were reported. Micro-ITT analysis population included all randomized subjects who had at least 1 gram negative typical pathogen (in the urine) at baseline known to cause cUTI and no gram cUTI and no gram positive pathogen (in the urine) at baseline.

End point type	Secondary

End point timeframe:

Baseline up to 50 days

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	23		
Units: percentage of subjects				
number (not applicable)	5.6	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Emergent Infections: Microbiologically Evaluable (ME) Analysis Population

End point title	Percentage of Subjects with Emergent Infections: Microbiologically Evaluable (ME) Analysis Population

End point description:

Emergent infections were categorized as super-infection and new infections. Superinfection: A urine

culture identified pathogen other than a baseline pathogen during the course of active treatment with study therapy along with worsening signs/ symptoms of infection requiring alternative antimicrobial therapy. New infection: A urine culture identified pathogen other than a baseline pathogen at any time after study treatment had finished along with worsening signs/symptoms of infection requiring alternative antimicrobial therapy. Percentage of subjects with any of the infections were reported. ME analysis set: subjects >=1gram(-ve) and no gram(+ve) pathogen (in urine) at baseline, confirmed cUTI diagnosis, had >=48hr IV study drug, unless discontinued due to AE, no important protocol deviation, concomitant antibiotic, >=1gram(-ve) typical UTI bacterial pathogen at Baseline susceptible to study drug and MR which was not indeterminate. ME analysis set.

End point type	Secondary

End point timeframe:

Baseline up to 50 days

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	16		
Units: percentage of subjects				
number (not applicable)	7.3	0		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Combined response was the combined assessment of clinical response and microbiological response. Favorable CR was defined as a CR of improvement and cure (at EOIV) and a CR of cure (at TOC). Cure defined as: resolution of all acute signs/symptoms of cUTI/improvement to such an extent that no further antimicrobial therapy required. Improvement defined as: subjects who switched to oral therapy and had afebrile(temperature<=38.0°C) for >=24 hr; absence of new and improvement in atleast 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline and worsening of none. Favourable MR was absence of the original baseline pathogen in source specimen. TOC visit occurred within 8 to 15 days after last dose of any study drug (IV or oral). Micro-ITT analysis population included all randomized subjects who had atleast 1 gram(-ve) typical pathogen(in the urine) at baseline known to cause cUTI and no gram cUTI and no gram(+ve) pathogen (in the urine) at baseline.

End point type	Secondary

End point timeframe:

EOIV visit (Day 4 to 15), TOC visit (up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	23		
Units: percentage of subjects				
number (not applicable)				
Favourable at EOIV	79.6	78.3		
Favourable at TOC	72.2	60.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Combined Response: Microbiologically Evaluable (ME) Analysis Population

End point title	Percentage of Subjects With Combined Response: Microbiologically Evaluable (ME) Analysis Population

End point description:

Combined response was the combined assessment of clinical response and microbiological response. Favorable clinical response was defined as a clinical response of improvement and cure (at EOIV) and a clinical response of cure (at TOC). Cure defined as: resolution of all acute signs/symptoms of cUTI/improvement to such an extent that no further antimicrobial therapy required. Improvement defined as: subjects who switched to oral therapy and had afebrile (temperature<=38.0°C) for >=24 hr; absence of new and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline and worsening of none. Favourable microbiological response was absence of the original baseline pathogen in source specimen. TOC visit occurred within 8 to 15 days after last dose of any study drug (IV or oral). ME analysis set. Here, 'n' signifies those subjects who were evaluable at specified time points, for each arm respectively.

End point type	Secondary

End point timeframe:

EOIV visit (Day 4 to 15), TOC visit (up to a maximum study duration of 50 days)

End point values	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	16		
Units: percentage of subjects				
number (not applicable)				
Favourable at EOIV (n=35, 16)	97.1	100		
Favourable at TOC (n=41, 16)	80.5	68.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline until the LFU visit (up to a maximum study duration of 50 days)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Ceftazidime- Avibactam (CAZ-AVI)

Reporting group description:

Subjects with Creatinine clearance(CrCL) >=50 milliliter per minute (mL/min) received single IV infusion of CAZ/AVI for 2 hour in following manner: 1)Age 12 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 to <12 years: 2000 mg CAZ/500 mg AVI (body weight >=40 kg), 50 mg/kg CAZ/12.5 mg/kg AVI (body weight <40 kg),3) Age 2 to <6 years: 50 mg/kg CAZ/12.5 mg/kg AVI, 4) Age <2 to 6 months: 50 mg/kg CAZ/12.5 mg/kg AVI, 5)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 14 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	Cefepime

Reporting group description:

Subjects received intravenous (IV) infusion of cefepime, at a dose and frequency prescribed by investigator's (maximum dose of cefepime in any single infusion not exceed 2000 mg every 12 hours). After having 72 hours of IV treatment, subjects had option to switch to an oral therapy at investigator's discretion.

Serious adverse events	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 67 (11.94%)	2 / 28 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 28 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 67 (2.99%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 67 (4.48%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ceftazidime-Avibactam (CAZ-AVI)	Cefepime	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 67 (19.40%)	9 / 28 (32.14%)	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 67 (2.99%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Diarrhoea			
subjects affected / exposed	5 / 67 (7.46%)	3 / 28 (10.71%)	
occurrences (all)	5	3	
Skin and subcutaneous tissue disorders			
Intertrigo			
subjects affected / exposed	1 / 67 (1.49%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	3 / 67 (4.48%)	2 / 28 (7.14%)	
occurrences (all)	4	2	
Infections and infestations			
Rhinitis			
subjects affected / exposed	4 / 67 (5.97%)	2 / 28 (7.14%)	
occurrences (all)	4	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2017	Added ITT and Micro-ITT analysis sets to the analysis in line with protocol amendment 2;Amended permissible visit windows for clinical and microbiological response; Added analysis of combined response; Updated derivation of age for patients with missing date of birth; Amended adverse events of special interest (AEoSI) to summarize by topic;Amended approach for summarising laboratory abnormality according to local lab criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported