# 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 | v1 |
| This version publication date | 28 March 2018 |
| First version publication date | 28 March 2018 |

## 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 | 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 |
| Country: Number of subjects enrolled | Taiwan: 17 |
| Country: Number of subjects enrolled | Turkey: 5 |
| Country: Number of subjects enrolled | United States: 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: Study is a single blinded study

| **Number of subjects in period 1** | Ceftazidime-Avibactam (CAZ-AVI) | Cefepime |
|---|---|---|
| Started | 68 | 29 |
| Treated | 67 | 28 |
| Completed | 64 | 26 |
| Not completed | 4 | 3 |
| Consent withdrawn by subject | 2 | - |
| Randomised but not treated | 1 | 1 |
| Lost to follow-up | 1 | 1 |
| Lack of efficacy | - | 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<br>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<br>Units: years | | | |
| arithmetic mean | 6.08 | 6.19 | |
| standard deviation | ± 5.647 | ± 6.072 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 57 | 22 | 79 |
| Male | 11 | 7 | 18 |
| Race (NIH/OMB)<br>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)<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 1 |
| Not Hispanic or Latino | 67 | 29 | 96 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Height<br>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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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 planned 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:

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 | 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 | 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 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.

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 28 (3.57%) | 2 / 67 (2.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 3 / 67 (4.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 28 (0.00%) | 1 / 67 (1.49%) | |
| 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** | Cefepime | Ceftazidime-Avibactam (CAZ-AVI) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 9 / 28 (32.14%) | 13 / 67 (19.40%) | |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 28 (7.14%)<br>2<br><br><br>3 / 28 (10.71%)<br>3 | <br><br>2 / 67 (2.99%)<br>2<br><br><br>5 / 67 (7.46%)<br>5 | |
| Skin and subcutaneous tissue disorders<br>Intertrigo<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 28 (7.14%)<br>2<br><br><br>2 / 28 (7.14%)<br>2 | <br><br>1 / 67 (1.49%)<br>1<br><br><br>3 / 67 (4.48%)<br>4 | |
| Infections and infestations<br>Rhinitis<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 28 (7.14%)<br>2 | <br><br>4 / 67 (5.97%)<br>4 | |

## 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