



Clinical trial results:

A Multicenter, Double-blind, Randomized, Clinical Study to Assess the Efficacy and Safety of Intravenous S-649266 in Complicated Urinary Tract Infections with or without Pyelonephritis or Acute Uncomplicated Pyelonephritis Caused by Gram-Negative Pathogens in Hospitalized Adults in Comparison with Intravenous Imipenem/Cilastatin

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2014-000914-76 |
| Trial protocol | CZ HU IT ES DE PL RO HR LV BG |
| Global end of trial date | 16 August 2016 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 02 September 2017 |
| First version publication date | 02 September 2017 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | 1409R2121 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02321800 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Shionogi Inc. |
| Sponsor organisation address | 300 Campus Drive, Florham Park, United States, NJ 07932 |
| Public contact | Simon Portsmouth, MD FRCP, Shionogi Inc., +1 973 307 3901, simon.portsmouth@shionogi.com |
| Scientific contact | Simon Portsmouth, MD FRCP, Shionogi Inc., +1 973 307 3901, simon.portsmouth@shionogi.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 November 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 July 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 August 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the composite outcome of microbiological eradication and clinical response of cefiderocol with that of imipenem/cilastatin (IPM/CS) in a subject population at risk for multidrug resistant (MDR) Gram-negative pathogens originating from complicated urinary tract infections (cUTIs) with or without pyelonephritis or acute uncomplicated pyelonephritis. The primary efficacy assessment was performed at the Test of Cure (TOC) (approximately 7 days following the End of Treatment [EOT]); (EOT is defined as the last day of study drug treatment).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. The rationale of the study, procedural details, and investigational goals were explained to each subject, along with potential risks and benefits. Each subject was assured of his/her right to withdraw from the study at any time.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 05 February 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 | Poland: 71 |
| Country: Number of subjects enrolled | Romania: 112 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | Croatia: 39 |
| Country: Number of subjects enrolled | Bulgaria: 23 |
| Country: Number of subjects enrolled | Czech Republic: 37 |
| Country: Number of subjects enrolled | Germany: 6 |
| Country: Number of subjects enrolled | Hungary: 26 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Latvia: 11 |
| Country: Number of subjects enrolled | Russian Federation: 74 |
| Country: Number of subjects enrolled | Georgia: 20 |
| Country: Number of subjects enrolled | Japan: 15 |
| Country: Number of subjects enrolled | United States: 7 |
| Worldwide total number of subjects | 452 |
| EEA total number of subjects | 336 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 214 |
| From 65 to 84 years | 226 |
| 85 years and over | 12 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period consists of the two days prior randomisation. Eligibility criteria were reviewed and qualified subjects providing informed consent entered the study.

Period 1

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

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | cefiderocol |

Arm description: -

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | cefiderocol |
| Investigational medicinal product code | S-649266 |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

2000 mg intravenously every 8 hours (6 or 8 hours based on renal function and/or body weight) for a period of 7 to 14 days.

| | |
|------------------|---------------------|
| Arm title | imipenem/cilastatin |
|------------------|---------------------|

Arm description: -

| | |
|--|----------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | imipenem/cilastatin (1000mg) |
| Investigational medicinal product code | IPM/CS 1000mg |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1000 mg intravenously every 8 hours (6 or 8 hours based on renal function and/or body weight) for a period of 7 to 14 days.

| Number of subjects in period 1 | cefiderocol | imipenem/cilastatin |
|---------------------------------------|-------------|---------------------|
| Started | 303 | 149 |
| Completed | 283 | 138 |
| Not completed | 20 | 11 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | 3 | 3 |

| | | |
|----------------------------|----|---|
| Adverse event, non-fatal | 2 | 3 |
| Randomized but not treated | 3 | 1 |
| Lost to follow-up | 10 | 4 |
| Protocol deviation | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------------|
| Reporting group title | cefiderocol |
| Reporting group description: - | |
| Reporting group title | imipenem/cilastatin |
| Reporting group description: - | |

| Reporting group values | cefiderocol | imipenem/cilastatin | Total |
|---|-------------|---------------------|-------|
| Number of subjects | 303 | 149 | 452 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 144 | 70 | 214 |
| From 65-84 years | 153 | 73 | 226 |
| 85 years and over | 6 | 6 | 12 |
| Age continuous Units: years | | | |
| arithmetic mean | 61.2 | 61.4 | |
| standard deviation | ± 16.5 | ± 17.8 | - |
| Gender categorical Units: Subjects | | | |
| Female | 165 | 83 | 248 |
| Male | 138 | 66 | 204 |

End points

End points reporting groups

| | |
|---|--------------------------------|
| Reporting group title | cefiderocol |
| Reporting group description: - | |
| Reporting group title | imipenem/cilastatin |
| Reporting group description: - | |
| Subject analysis set title | mITT Population (cefiderocol) |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All ITT patients who have a baseline Gram-negative bacterial uropathogen on culture of urine or blood that causes UTI and have received the study drug cefiderocol. Patients should not be excluded from this population based upon events that occurred post randomization (eg, loss to follow-up). | |
| Subject analysis set title | mITT Population (IPM/CS) |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All ITT patients who have a baseline Gram-negative bacterial uropathogen on culture of urine or blood that causes UTI and have received the active comparator IPM/CS. Patients should not be excluded from this population based upon events that occurred post randomization (eg, loss to follow-up). | |

Primary: Composite of clinical outcome and microbiological outcome at TOC

| | |
|---|--|
| End point title | Composite of clinical outcome and microbiological outcome at TOC |
| End point description: | |
| End point type | Primary |
| End point timeframe: From Baseline to Test of Cure (TOC) | |

| End point values | mITT Population (cefiderocol) | mITT Population (IPM/CS) | | |
|---------------------------------|--------------------------------|--------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 252 | 119 | | |
| Units: Proportion of responders | | | | |
| number (not applicable) | 183 | 65 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Proportion of Responders |
| Comparison groups | mITT Population (cefiderocol) v mITT Population (IPM/CS) |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 371 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Proportion difference |
| Point estimate | 18.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.23 |
| upper limit | 28.92 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of informed consent through 28 days (\pm 3 days) after the last dose of the study drug.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | cefiderocol |
|-----------------------|-------------|

Reporting group description: -

| | |
|-----------------------|---------------------|
| Reporting group title | Imipenem/Cilastatin |
|-----------------------|---------------------|

Reporting group description: -

| Serious adverse events | cefiderocol | Imipenem/Cilastatin | |
|--|------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 300 (4.67%) | 12 / 148 (8.11%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Urethrotomy | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematocrit decreased | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal injury | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Congenital ureteric anomaly | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Gallbladder pain | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (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 | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive nephropathy | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (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 | | | |
| Abscess | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascariasis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 2 / 148 (1.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic abscess | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 148 (0.68%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal abscess | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 148 (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: 2 %

| Non-serious adverse events | cefiderocol | Imipenem/Cilastatin | |
|---|--------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 118 / 300 (39.33%) | 72 / 148 (48.65%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 13 / 300 (4.33%) | 8 / 148 (5.41%) | |
| occurrences (all) | 13 | 8 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 300 (2.33%) | 8 / 148 (5.41%) | |
| occurrences (all) | 7 | 8 | |
| General disorders and administration site conditions | | | |
| Infusion site erythema | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 3 / 148 (2.03%) | |
| occurrences (all) | 3 | 3 | |
| Infusion site pain | | | |
| subjects affected / exposed | 9 / 300 (3.00%) | 5 / 148 (3.38%) | |
| occurrences (all) | 9 | 5 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 5 / 148 (3.38%) | |
| occurrences (all) | 2 | 5 | |
| Constipation | | | |
| subjects affected / exposed | 10 / 300 (3.33%) | 6 / 148 (4.05%) | |
| occurrences (all) | 10 | 6 | |
| Diarrhoea | | | |

| | | | |
|--|------------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 12 / 300 (4.00%) 12 | 8 / 148 (5.41%) 8 | |
| Nausea subjects affected / exposed occurrences (all) | 7 / 300 (2.33%) 7 | 6 / 148 (4.05%) 6 | |
| Vomiting subjects affected / exposed occurrences (all) | 6 / 300 (2.00%) 6 | 2 / 148 (1.35%) 2 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 7 / 300 (2.33%) 7 | 1 / 148 (0.68%) 1 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 4 / 300 (1.33%) 4 | 3 / 148 (2.03%) 3 | |
| Renal and urinary disorders Renal cyst subjects affected / exposed occurrences (all) | 4 / 300 (1.33%) 4 | 5 / 148 (3.38%) 5 | |
| Infections and infestations Clostridium difficile colitis subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 3 / 148 (2.03%) 3 | |
| Vaginal infection subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 3 / 148 (2.03%) 3 | |
| Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all) | 5 / 300 (1.67%) 5 | 4 / 148 (2.70%) 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 05 August 2015 | <ul style="list-style-type: none">•Modified wording describing the primary objective, clarifying that the primary comparison is a composite outcome and not clinical or microbiological responses individually•Clarified subject population (including restriction/stratification of subjects with uncomplicated pyelonephritis, number of pathogens that could be present in urine), duration of treatment, dose adjustment (based on Cockcroft-Gault equation)•Clarified period during which women should not attempt to get pregnant after study drug administration and also allowed for country specific requirements, which might be longer•Clarified "the what and the why" for prohibited medications•Clarified components of clinical evaluation and microbiological response•Clarified statistical section, incorporated 15% noninferiority margin, defined populations, clarified sample size, and clarified stratification at randomization•Clarified function of the DSMB as performing a safety evaluation and not an interim analysis of efficacy•Clarified that treatment duration of 7 to 14 days in hospital may be shortened to 5 days if it became in the subject's best interest•Clarified minimum versus recommended treatment duration•Adjusted dosing tables to include dosing instructions for subjects weighing <40kg•Clarified the need to record all concomitant antimicrobial therapies and time frame involved, and reinforced that the use of antimicrobial therapies with only Gram-positive activities were allowed if needed; clarified timing for withdrawal and restarting these therapies in relation to treatment; added details for use of rescue therapy and prophylactic antimicrobials•Added Subject Structured Interview and changed terminology to "Structured Patient Interview" for consistency•Clarified definition of AEs in the context of study, study treatment, and population•Clarified follow-up time for SAEs, reporting time for pregnancy, and reasons for discontinuation•Specified timing of ECG in relation to infusion |
| 30 November 2015 | <ul style="list-style-type: none">• Increased the number of subjects (from 300 to 400) so that this study would provide the majority of subjects for the safety evaluation of the drug for the submission to the FDA• Increased the number of subjects with acute uncomplicated pyelonephritis and the time required for enrollment and revised statistical evaluation description• Allowed for collection of available safety laboratory information that may have been available prior to the subject entering the study, ie, prior to any drug treatment for subjects with previous short term antibiotic treatment (< 24 hours)• Clarified what needed to be completed in the event that a super infection or a new infection was identified• Clarified the primary analysis and the method of arriving at the result |
| 26 April 2016 | <ul style="list-style-type: none">• Increased the number of subjects (from 400 to 450) so that this study would provide sufficient safety subjects for submission to the FDA (for a total of 300 subjects treated with cefiderocol)• Increased the number of subjects with acute uncomplicated pyelonephritis and the time required for enrollment and revised statistical evaluation description |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported