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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2015	•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	• 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	• 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