Clinical trial results:
A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens

Summary

EudraCT number	2015-004703-23
Trial protocol	ES DE GR GB HR FR IT
Global end of trial date	22 April 2019

Results information

Result version number	v1 (current)
This version publication date	07 May 2020
First version publication date	07 May 2020

Trial information

Trial identification

Sponsor protocol code	1424R2131

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Shionogi B.V.
Sponsor organisation address	Kingsfordweg 151, Amsterdam , Netherlands, 1043GR
Public contact	Corporate Communications Department, Shionogi & Co., Ltd, 0081 6 6209 7885, shionogiclintrials-admin@shionogi.co.jp
Scientific contact	Corporate Communications Department, Shionogi & Co., Ltd, 0081 6 6209 7885, shionogiclintrials-admin@shionogi.co.jp

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	28 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2019
Global end of trial reached?	Yes
Global end of trial date	22 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To assess, at test of cure (TOC), the clinical outcome of treatment with S-649266 or best available therapy (BAT) in adult patients with either hospital acquired pneumonia (HAP)/ventilator associated pneumonia (VAP)/healthcare-associated pneumonia (HCAP) or bloodstream infections/sepsis (BSI/sepsis) caused by carbapenem-resistant Gram-negative pathogens
-To assess, at TOC, the microbiologic outcome of treatment with S-649266 or BAT in adult patients with complicated urinary tract infection (cUTI) caused by carbapenem-resistant Gram-negative pathogens

Protection of trial subjects:

After the study began, a Medical Review Committee (MRC) was convened to review mortality data imbalances that had been observed in the study. Later, an independent DSMB was established for this study. Details of the DSMB composition, roles, responsibilities, and processes are documented in a separate DSMB charter. The DSMB reviewed subject information (efficacy and safety) periodically and immediately in the event of a death. However, the timing and the frequency of DSMB reviews and meetings were adjusted as needed, as decided by the DSMB members.

Background therapy: -

Evidence for comparator:

The control population was treated with best available therapy (BAT), locally sourced by study sites, within the local standard of care determined by the investigator for each infection diagnosis prior to randomization. This consisted of 1 to 3 antibiotic agents selected specifically for the carbapenem-resistant Gram-negative pathogen. Published clinical studies, usually retrospective or nonrandomized observational studies, have not shown conclusively that combinations of antibiotics are superior to monotherapy.
Results of these studies are highly variable and often dependent on the type of infection or the specific causative pathogen

Actual start date of recruitment	07 September 2016
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	Japan: 2
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Croatia: 3

Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Guatemala: 8
Country: Number of subjects enrolled	Israel: 36
Worldwide total number of subjects	152
EEA total number of subjects	32

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)	65
From 65 to 84 years	78
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

A total of 258 subjects were screened at 60 study centers in North America, South America, Europe, Middle East, and Asia. Of these, 105 subjects were excluded as screen failures.

Pre-assignment

Screening details:

Male or female subjects 18 years of age or older who had a documented infection caused by a carbapenem-resistant Gram-negative pathogen and who required hospitalization for the parenteral (IV) treatment of the infection were enrolled in the study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cefiderocol

Arm description:

Cefiderocol (1 g/vial) as a lyophilized powder for dilution for IV administration. Cefiderocol 2 g administered intravenously every 8 hours as a 3-hour infusion with/without another single adjunctive Gram-negative antibiotic other than a polymyxin or a cephalosporin/carbapenem including combination with β-lactamase inhibitor (eg, ceftazidime/avibactam or ceftolozane/tazobactam)

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

Dosage and administration details:

Cefiderocol 2 g administered intravenously every 8 hours as a 3-hour infusion with/without another single adjunctive Gram-negative antibiotic other than a polymyxin or a cephalosporin/carbapenem including combination with β-lactamase inhibitor (eg, ceftazidime/avibactam or ceftolozane/tazobactam)

Arm title	Best Available Therapy

Arm description:

Investigator-determined Best available therapy (BAT). Standard of care with either a polymyxin-based or nonpolymyxin-based regimen as determined by the investigator and consisting of 1 to 3 marketed antibacterial agent(s).

Arm type	Control treatment regimen
Investigational medicinal product name	Polymyxin-based or nonpolymyxin-based regimen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dosage of BAT and adjunctive antibiotic therapy is based on the country specific package insert(s) and the discretion of the investigator. Adjustments for renal impairment will be made according to each product label.The administration schedule of study after initial administration may be adjusted

gradually, within reason and based on the clinical judgement of the investigator to fit the routine treatment schedules of the investigator's hospital as long as the dosing intervals and infusion durations indicated by the protocol are maintained following adjustment.

Number of subjects in period 1	Cefiderocol	Best Available Therapy
Started	101	51
Completed	69	38
Not completed	32	13
Adverse event, serious fatal	30	9
Consent withdrawn by subject	-	2
withdrawal by subject	1	-
other	-	1
Lost to follow-up	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cefiderocol
Reporting group description:	
Cefiderocol (1 g/vial) as a lyophilized powder for dilution for IV administration. Cefiderocol 2 g administered intravenously every 8 hours as a 3-hour infusion with/without another single adjunctive Gram-negative antibiotic other than a polymyxin or a cephalosporin/carbapenem including combination with β-lactamase inhibitor (eg, ceftazidime/avibactam or ceftolozane/tazobactam)	
Reporting group title	Best Available Therapy
Reporting group description:	
Investigator-determined Best available therapy (BAT). Standard of care with either a polymyxin-based or nonpolymyxin-based regimen as determined by the investigator and consisting of 1 to 3 marketed antibacterial agent(s).	

Reporting group values	Cefiderocol	Best Available Therapy	Total
Number of subjects	101	51	152
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
Less than 65 years	37	28	65
65 years and over	64	23	87
Gender categorical Units: Subjects			
Female	35	14	49
Male	66	37	103

Subject analysis sets	
Subject analysis set title	CR - Micro Intent to treat Cefiderocol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Carbapenem-resistant Microbiological Intent-to-treat (CR-mITT) population: All subjects in the ITT population who had a Carbapenem-resistant baseline Gram-negative pathogen from an appropriate clinical specimen.	
Subject analysis set title	CR - Micro Intent to treat BAT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Carbapenem-resistant Microbiological Intent-to-treat (CR-mITT) population: Microbiological Intent-to-treat (Micro-ITT) population: all subjects in the ITT population who had a baseline Gram-negative pathogen from an appropriate clinical specimen.	
Subject analysis set title	Safety population cefiderocol
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who receive at least one dose of cefiderocol.

Subject analysis set title	Safety population BAT
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who receive at least one dose of BAT

Subject analysis set title	CR - mITT HAP/VAP/HCAP for cefiderocol
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing receiving cefiderocol

Subject analysis set title	CR - mITT HAP/VAP/HCAP for BAT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing, receiving BAT

Subject analysis set title	CR - mITT BSI/sepsis for cefiderocol
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing receiving cefiderocol

Subject analysis set title	CR - mITT BSI/sepsis for BAT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing receiving BAT

Subject analysis set title	CR - mITT cUTI for cefiderocol
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing receiving cefiderocol

Subject analysis set title	CR - mITT cUTI for BAT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing receiving BAT

Reporting group values	CR - Micro Intent to treat Cefiderocol	CR - Micro Intent to treat BAT	Safety population cefiderocol
Number of subjects	80	38	101
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
Less than 65 years	30	21	37
65 years and over	50	17	64
Gender categorical Units: Subjects			
Female	25	9	35

Male	55	29	66

Reporting group values	Safety population BAT	CR - mITT HAP/VAP/HCAP for cefiderocol	CR - mITT HAP/VAP/HCAP for BAT
Number of subjects	49	40	19
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
Less than 65 years	27	14	10
65 years and over	22	26	9
Gender categorical Units: Subjects			
Female	14	13	2
Male	35	27	17

Reporting group values	CR - mITT BSI/sepsis for cefiderocol	CR - mITT BSI/sepsis for BAT	CR - mITT cUTI for cefiderocol
Number of subjects	23	14	17
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
Less than 65 years	11	8	5
65 years and over	12	6	12
Gender categorical Units: Subjects			
Female	8	5	4
Male	15	9	13

Reporting group values	CR - mITT cUTI for BAT		
Number of subjects	5		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Less than 65 years	3		
65 years and over	2		
Gender categorical Units: Subjects			
Female	2		
Male	3		

End points

End points reporting groups

Reporting group title	Cefiderocol

Reporting group description:

Cefiderocol (1 g/vial) as a lyophilized powder for dilution for IV administration. Cefiderocol 2 g administered intravenously every 8 hours as a 3-hour infusion
with/without another single adjunctive Gram-negative antibiotic other than a polymyxin or a cephalosporin/carbapenem including combination with β-lactamase
inhibitor (eg, ceftazidime/avibactam or ceftolozane/tazobactam)

Reporting group title	Best Available Therapy

Reporting group description:

Investigator-determined Best available therapy (BAT). Standard of care with either a polymyxin-based or nonpolymyxin-based regimen as determined by the investigator and consisting of 1 to 3 marketed antibacterial agent(s).

Subject analysis set title	CR - Micro Intent to treat Cefiderocol
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Carbapenem-resistant Microbiological Intent-to-treat (CR-mITT) population: All subjects in the ITT population who had a Carbapenem-resistant baseline Gram-negative pathogen from an appropriate clinical specimen.

Subject analysis set title	CR - Micro Intent to treat BAT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Carbapenem-resistant Microbiological Intent-to-treat (CR-mITT) population: Microbiological Intent-to-treat (Micro-ITT) population: all subjects in the ITT population who had a baseline Gram-negative pathogen from an appropriate clinical specimen.

Subject analysis set title	Safety population cefiderocol
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who receive at least one dose of cefiderocol.

Subject analysis set title	Safety population BAT
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects who receive at least one dose of BAT

Subject analysis set title	CR - mITT HAP/VAP/HCAP for cefiderocol
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen
was carbapenem-resistant as confirmed by central laboratory testing receiving cefiderocol

Subject analysis set title	CR - mITT HAP/VAP/HCAP for BAT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen
was carbapenem-resistant as confirmed by central laboratory testing, receiving BAT

Subject analysis set title	CR - mITT BSI/sepsis for cefiderocol
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen
was carbapenem-resistant as confirmed by central laboratory testing receiving cefiderocol

Subject analysis set title	CR - mITT BSI/sepsis for BAT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen
was carbapenem-resistant as confirmed by central laboratory testing receiving BAT

Subject analysis set title	CR - mITT cUTI for cefiderocol
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing receiving cefiderocol

Subject analysis set title	CR - mITT cUTI for BAT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing receiving BAT

Primary: Clinical Outcome - HAP/VAP/HCAP at TOC

End point title	Clinical Outcome - HAP/VAP/HCAP at TOC[1]

End point description:

Analysis of the primary efficacy endpoint for subjects with HAP/VAP/HCAP clinical outcome at TOC (clinical cure, clinical failure, or indeterminate) for the CR Micro-ITT population.

End point type	Primary

End point timeframe:

Test-of-cure (TOC)

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: Calculating descriptive analysis is pre-specified, but no inferential testing was planned. Therefore no treatment comparisons were done in this study.

End point values	CR - mITT HAP/VAP/HCAP for cefiderocol	CR - mITT HAP/VAP/HCAP for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	19		
Units: 59				
Eradication	20	10		
Persistence	16	6		
Indeterminate	4	3		

Statistical analyses

No statistical analyses for this end point

Primary: Clinical outcome - BSI/Sepsis at TOC

End point title	Clinical outcome - BSI/Sepsis at TOC[2]

End point description:

Analysis of the primary efficacy endpoint for subjects with BSI/sepsis, clinical outcome at TOC (clinical cure, clinical failure, or indeterminate) for the CR Micro-ITT population,

End point type	Primary

End point timeframe:

Test-of-Cure (TOC)

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: Calculating descriptive analysis is pre-specified, but no inferential testing was planned. Therefore no treatment comparisons were done in this study.

End point values	CR - mITT BSI/sepsis for cefiderocol	CR - mITT BSI/sepsis for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	14		
Units: 37				
Eradication	10	6		
Persistence	9	7		
Indeterminate	4	1		

Statistical analyses

No statistical analyses for this end point

Primary: Microbiological outcome - cUTI at TOC

End point title	Microbiological outcome - cUTI at TOC[3]

End point description:

Analysis of the primary efficacy endpoint for subjects with cUTI, microbiological outcome for Gram-negative pathogen at TOC (eradication, persistence, or indeterminate),

End point type	Primary

End point timeframe:

Test-of-cure (TOC)

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: Calculating descriptive analysis is pre-specified, but no inferential testing was planned. Therefore no treatment comparisons were done in this study.

End point values	CR - mITT cUTI for cefiderocol	CR - mITT cUTI for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	5		
Units: 22				
Eradication	9	1		
Persistence	5	1		
Indeterminate	3	3		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical outcome - HAP/VAP/HCAP at EoT

End point title	Clinical outcome - HAP/VAP/HCAP at EoT

End point description:

Analysis of the efficacy endpoint for subjects with HAP/VAP/HCAP clinical outcome at EoT (clinical cure, clinical failure, or indeterminate) for the CR Micro-ITT population.

End point type	Other pre-specified

End point timeframe:

End of Treatment (EoT)

End point values	CR - mITT HAP/VAP/HCAP for cefiderocol	CR - mITT HAP/VAP/HCAP for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	19		
Units: 59				
Eradication	24	12		
Persistence	13	7		
Indeterminate	3	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical outcome - HAP/VAP/HCAP at FU

End point title	Clinical outcome - HAP/VAP/HCAP at FU

End point description:

Analysis of the efficacy endpoint for subjects with HAP/VAP/HCAP clinical outcome at FU (sustained clinical cure, relapse, clinical failure, or indeterminate) for the CR Micro-ITT population.

End point type	Other pre-specified

End point timeframe:

Follow-Up (FU)

End point values	CR - mITT HAP/VAP/HCAP for cefiderocol	CR - mITT HAP/VAP/HCAP for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	19		
Units: 59				
Sustained eradication	20	6		
Recurrence	0	3		
Persistence	16	6		
indeterminate	4	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical outcome - BSI/Sepsis at EoT

End point title	Clinical outcome - BSI/Sepsis at EoT

End point description:

Analysis of the efficacy endpoint for subjects with BSI/sepsis, clinical outcome at EoT (clinical cure, clinical failure, or indeterminate) for the CR Micro-ITT population.

End point type	Other pre-specified

End point timeframe:

End of treatment (EoT)

End point values	CR - mITT BSI/sepsis for cefiderocol	CR - mITT BSI/sepsis for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	14		
Units: 37				
Eradication	16	7		
Persistence	6	7		
Indeterminate	1	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical outcome - BSI/Sepsis at FU

End point title	Clinical outcome - BSI/Sepsis at FU

End point description:

Analysis of the efficacy endpoint for subjects with BSI/sepsis, clinical outcome at FU (sustained clinical cure, relapse, clinical failure, or indeterminate) for the CR Micro-ITT population,

End point type	Other pre-specified

End point timeframe:

Follow-Up (FU)

End point values	CR - mITT BSI/sepsis for cefiderocol	CR - mITT BSI/sepsis for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	14		
Units: 37				
Sustained eradication	9	4		
Recurrence	1	1		
Persistence	9	7		

Indeterminate	4	2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Microbiological outcome - cUTI at EoT

End point title	Microbiological outcome - cUTI at EoT

End point description:

Analysis of the efficacy endpoint for subjects with cUTI, microbiological outcome for Gram-negative pathogen at EoT (eradication, persistence, or indeterminate).

End point type	Other pre-specified

End point timeframe:

End of treatment (EoT)

End point values	CR - mITT cUTI for cefiderocol	CR - mITT cUTI for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	5		
Units: 22				
Eradication	12	1		
Persistence	0	0		
Indeterminate	5	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Microbiological outcome - cUTI at FU

End point title	Microbiological outcome - cUTI at FU

End point description:

Analysis of the efficacy endpoint for subjects with cUTI, microbiological outcome for Gram-negative pathogen at FU(sustained eradication, recurrence, persistence, or indeterminate).

End point type	Other pre-specified

End point timeframe:

Follow-up (FU)

End point values	CR - mITT cUTI for cefiderocol	CR - mITT cUTI for BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	5		
Units: 22				
Sustained eradication	7	1		
Recurrence	0	0		
Persistence	5	1		
Indeterminate	5	3		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Microbiological outcome - All Infection Sites at TOC

End point title	Microbiological outcome - All Infection Sites at TOC

End point description:

Analysis of the efficacy endpoint for all infection sites, microbiological outcome for Gram-negative pathogen at TOC (eradication, persistence, or indeterminate),

End point type	Other pre-specified

End point timeframe:

Test-of-cure (TOC)

End point values	CR - Micro Intent to treat Cefiderocol	CR - Micro Intent to treat BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	38		
Units: 118				
Eradication	25	9		
Persistence	16	10		
Indeterminate	39	19		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Microbiolocial outcome - All Infection Sites at EoT

End point title	Microbiolocial outcome - All Infection Sites at EoT

End point description:

Analysis of the efficacy endpoint in all infection sites, microbiological outcome for Gram-negative pathogen at EoT (eradication, persistence, or indeterminate).

End point type	Other pre-specified

End point timeframe:

End of treatment (EoT)

End point values	CR - Micro Intent to treat Cefiderocol	CR - Micro Intent to treat BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	38		
Units: 118				
Eradication	38	10		
Persistence	16	10		
Indeterminate	26	18		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Microbiological outcome - All Infection Sites at FU

End point title	Microbiological outcome - All Infection Sites at FU

End point description:

Analysis of the efficacy endpoint in all infection sites, microbiological outcome for Gram-negative pathogen at FU (sustained eradication, recurrence, persistence, or indeterminate).

End point type	Other pre-specified

End point timeframe:

Follow-up (FU)

End point values	CR - Micro Intent to treat Cefiderocol	CR - Micro Intent to treat BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	38		
Units: 118				
Sustained eradication	21	7		
Recurrence	0	1		
Persistence	16	10		
Indeterminate	43	20		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical outcome - All Infection sites at TOC

End point title	Clinical outcome - All Infection sites at TOC

End point description:

Analysis of the efficacy endpoint for all infection sites, clinical outcome at TOC (clinical cure, clinical failure, or indeterminate) for
the CR Micro-ITT population.

End point type	Other pre-specified

End point timeframe:

Tes-of-cure (TOC)

End point values	CR - Micro Intent to treat Cefiderocol	CR - Micro Intent to treat BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	38		
Units: 118				
Clinical Cure	42	19		
Clinical Failure	27	14		
Indeterminate	11	5		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical outcome - All infection sites at EoT

End point title	Clinical outcome - All infection sites at EoT

End point description:

Analysis of the efficacy endpoint for all infection sites, clinical outcome at EoT (clinical cure, clinical failure, or indeterminate) for
the CR Micro-ITT population.

End point type	Other pre-specified

End point timeframe:

End of treatment (EoT)

End point values	CR - Micro Intent to treat Cefiderocol	CR - Micro Intent to treat BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	38		
Units: 118				
Clinical Cure	53	22		
Clinical Failure	20	15		
Indeterminate	7	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical outcome - All infection sites at FU

End point title	Clinical outcome - All infection sites at FU

End point description:

Analysis of the efficacy endpoint for all infection sites, clinical outcome at FU (clinical cure, clinical failure, or indeterminate) for
the CR Micro-ITT population.

End point type	Other pre-specified

End point timeframe:

Follow-Up (FU)

End point values	CR - Micro Intent to treat Cefiderocol	CR - Micro Intent to treat BAT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	38		
Units: 118				
Sustained clinical cure	38	13		
Relapse	2	4		
Clinical failure	27	14		
Indeterminate	13	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events described in this report were treatment-emergent AEs (ie, presented or worsened after administration of study treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	cefiderocol - safety
Reporting group description: -	
Reporting group title	BAT - Safety

Reporting group description: -

Serious adverse events	cefiderocol - safety	BAT - Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 101 (49.50%)	23 / 49 (46.94%)	
number of deaths (all causes)	34	9	
number of deaths resulting from adverse events	34	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	4 / 101 (3.96%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Generalised oedema			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
multi-organ failure			
subjects affected / exposed	2 / 101 (1.98%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pyrexia			
subjects affected / exposed	3 / 101 (2.97%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 101 (0.99%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Obstructive airways disorder			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 101 (1.98%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary cavitation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory acidosis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory failure			
subjects affected / exposed	3 / 101 (2.97%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 101 (3.96%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	2 / 101 (1.98%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transaminases increased			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 101 (1.98%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	4 / 101 (3.96%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 2	
Cardiac failure congestive			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (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			
Neurological decompensation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Quadriplegia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Retroperitoneal lymphadenopathy			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (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	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Chronic hepatic failure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (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	4 / 101 (3.96%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 4	2 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Anuria			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Oliguria			
subjects affected / exposed	2 / 101 (1.98%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Renal tubular acidosis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	2 / 101 (1.98%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Device related infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Empyema			
subjects affected / exposed	1 / 101 (0.99%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Enterococcal bacteraemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	2 / 101 (1.98%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 101 (5.94%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	3 / 101 (2.97%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Septic shock			

subjects affected / exposed	13 / 101 (12.87%)	6 / 49 (12.24%)	
occurrences causally related to treatment / all	0 / 13	1 / 6	
deaths causally related to treatment / all	0 / 11	0 / 3	
Staphylococcal infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolic acidosis			
subjects affected / exposed	3 / 101 (2.97%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	cefiderocol - safety	BAT - Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 101 (91.09%)	47 / 49 (95.92%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 101 (6.93%)	0 / 49 (0.00%)	
occurrences (all)	7	0	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 101 (7.92%)	1 / 49 (2.04%)	
occurrences (all)	8	1	
Liver function test abnormal			

subjects affected / exposed	8 / 101 (7.92%)	4 / 49 (8.16%)	
occurrences (all)	8	4	
Vascular disorders			
Hypotension			
subjects affected / exposed	8 / 101 (7.92%)	3 / 49 (6.12%)	
occurrences (all)	8	3	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	3 / 101 (2.97%)	3 / 49 (6.12%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	5 / 101 (4.95%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Pyrexia			
subjects affected / exposed	14 / 101 (13.86%)	6 / 49 (12.24%)	
occurrences (all)	14	6	
Chest pain			
subjects affected / exposed	6 / 101 (5.94%)	0 / 49 (0.00%)	
occurrences (all)	6	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 101 (7.92%)	2 / 49 (4.08%)	
occurrences (all)	8	2	
Thrombocytopenia			
subjects affected / exposed	6 / 101 (5.94%)	4 / 49 (8.16%)	
occurrences (all)	6	4	
Hyperkalaemia			
subjects affected / exposed	5 / 101 (4.95%)	6 / 49 (12.24%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 101 (18.81%)	6 / 49 (12.24%)	
occurrences (all)	19	6	
Vomiting			

subjects affected / exposed	13 / 101 (12.87%)	7 / 49 (14.29%)	
occurrences (all)	13	7	
Constipation			
subjects affected / exposed	8 / 101 (7.92%)	3 / 49 (6.12%)	
occurrences (all)	8	3	
Nausea			
subjects affected / exposed	7 / 101 (6.93%)	2 / 49 (4.08%)	
occurrences (all)	7	2	
Abdominal pain			
subjects affected / exposed	6 / 101 (5.94%)	4 / 49 (8.16%)	
occurrences (all)	6	4	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	8 / 101 (7.92%)	1 / 49 (2.04%)	
occurrences (all)	8	1	
Dyspnoea			
subjects affected / exposed	7 / 101 (6.93%)	2 / 49 (4.08%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 101 (2.97%)	4 / 49 (8.16%)	
occurrences (all)	3	4	
Decubitus ulcer			
subjects affected / exposed	10 / 101 (9.90%)	4 / 49 (8.16%)	
occurrences (all)	10	4	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	7 / 101 (6.93%)	5 / 49 (10.20%)	
occurrences (all)	7	5	
Psychiatric disorders			
Agitation			
subjects affected / exposed	5 / 101 (4.95%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Insomnia			
subjects affected / exposed	2 / 101 (1.98%)	3 / 49 (6.12%)	
occurrences (all)	2	3	

Depression			
subjects affected / exposed	0 / 101 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Infections and infestations			
Sepsis			
subjects affected / exposed	4 / 101 (3.96%)	3 / 49 (6.12%)	
occurrences (all)	4	3	
Septic shock			
subjects affected / exposed	13 / 101 (12.87%)	7 / 49 (14.29%)	
occurrences (all)	13	7	
Pneumonia			
subjects affected / exposed	7 / 101 (6.93%)	1 / 49 (2.04%)	
occurrences (all)	7	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	9 / 101 (8.91%)	7 / 49 (14.29%)	
occurrences (all)	9	7	
Metabolic acidosis			
subjects affected / exposed	3 / 101 (2.97%)	3 / 49 (6.12%)	
occurrences (all)	3	3	
Hypomagnesaemia			
subjects affected / exposed	6 / 101 (5.94%)	4 / 49 (8.16%)	
occurrences (all)	6	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2016	Amendment 1 (Version 2, 18 Jan 2016) added HCAP to the targeted types of pneumonia; added safety assessments to be performed on Day 14 if treatment duration was extended up to 21 days; removed cUTI from the primary endpoint of clinical outcome at TOC (because the primary endpoint for cUTI is microbiological outcome at TOC); added results of independent Data Safety Monitoring Board (DSMB) evaluation of the first 100 subjects who had completed the Phase 2 Study R2121; and provided additional guidance for assessing and capturing ventilator parameters and clinical signs and symptoms of infection, including infection-specific signs/symptoms
09 November 2016	Amendment 2 (Version 3, 09 Nov 2016) added the approved International Nonproprietary Name (INN) (cefiderocol); better defined the inclusion criterion for subjects who had failed empiric therapy; added a new exclusion criterion for subjects receiving peritoneal dialysis; add Chromogenic Media to the methods that could be used to provide evidence of carbapenem-resistant bacteria; established procedures for a subject to have therapy for longer than 21 days if needed; added a section with management criteria for laboratory abnormalities; provided sites with additional guidance on preplanned or elective procedures; updated preferred SAE reporting procedure to EDC; removed need to collect pregnancy information on female partners of male subjects. A country-specific version of the protocol was prepared for France.
16 November 2017	Amendment 3 (Version 4, 16 Nov 2017) added new study results/information; the contents of several clarification letters sent to the study sites; clarified the need for a chest autoradiograph of CT scan to establish the presence of pneumonia; clarified the requirement for clinical specimens prior to the start of infusion of drug treatment; changed 1 of the criteria for eradication (cUTI) from < 104 CFU/mL to < 103 CFU/mL in urine culture; clarified times during which AEs were assessed and what determined the expectedness of an AE; added serum iron to the list of specialized tests; initiated a DSMB to replace the ad-hoc Medical Review Committee (MRC) that was convened to address deaths occurring in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

20 September 2017	An imbalance in mortality in the cefiderocol arm compared to the BAT arm was observed in the study, leading to the Sponsor notifying a voluntary temporary halt of the trial enrollment on the 22nd of September 2017 in all participating countries in order to investigate the imbalance and review all data available both internally and with external experts. Shionogi and the Principal Investigators in this study independently determined that the reported fatalities did not constitute Suspected Unexpected Serious Adverse Reactions ("SUSARs") and that they were deemed to be not related to cefiderocol by the investigators and by Shionogi. Shionogi initiated a DSMB for an independent assessment of all available data from this study which provided regular safety reviews.	30 October 2017

Notes:

Limitations and caveats

None reported