



Clinical trial results:

A Multicenter, Randomized, Double-blind, Parallel-group, Clinical Study of S-649266 Compared with Meropenem for the Treatment of Hospital-acquired Bacterial Pneumonia, Ventilator-associated Bacterial Pneumonia, or Healthcare-associated Bacterial Pneumonia Caused by Gram-negative Pathogens

Summary

EudraCT number	2016-003020-23
Trial protocol	CZ GB LV HU ES BE
Global end of trial date	01 April 2019

Results information

Result version number	v1 (current)
This version publication date	16 April 2020
First version publication date	16 April 2020

Trial information

Trial identification

Sponsor protocol code	1615R2132
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03032380
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shionogi B.V.
Sponsor organisation address	Kingsfordweg 151, 1043 GR Amsterdam, Netherlands,
Public contact	Corporate Communications Department, Shionogi & Co., Ltd , +81 66209 7885, shionogiclintrials-admin@shionogi.co.jp
Scientific contact	Corporate Communications Department, Shionogi & Co., Ltd , +81 66209 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	01 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2019
Global end of trial reached?	Yes
Global end of trial date	01 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare all-cause mortality at Day 14 of subjects who receive S-649266 with that of subjects who receive the comparator, meropenem, in adults with hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP) caused by Gram-negative pathogens

Protection of trial subjects:

An independent DSMB was established for this study. Interim analyses were performed to review unblinded safety and efficacy data after approximately 50 and 150 subjects were randomized and had completed treatment and follow-up. After the unblinded review of the first 50 subjects by the DSMB, a request was made to have an additional unblinded review of safety and efficacy data after 100 subjects were randomized into the study. Because most of the subjects were already enrolled at the time of the DSMB meeting for 100 subjects, the DSMB also reviewed up-to-date unblinded mortality data for 232 subjects.

Background therapy: -

Evidence for comparator:

Meropenem was chosen as the comparator based on the American Thoracic Society/Infectious Disease Society guidelines of 2004 as an option for initial combination empiric therapy at a dosage of 1 g IV q8h in subjects with late-onset disease or risk factors for multidrug-resistant (MDR) pathogens. The dosage of meropenem administered and the duration of treatment took into account the type and severity of infection to be treated and the clinical response to treatment. The SmPC indicates that a dose of up to 2 g given 3 times daily in adults and adolescents may be particularly appropriate when treating some types of infections, such as infections due to less susceptible bacterial species (eg, Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter* spp.) or very severe infections. The dosage of meropenem was 2 g q8h infused IV over 3 hours to ensure the highest probability of bactericidal target attainment (40% $fT > MIC$), which is important especially in less susceptible bacterial species.

Actual start date of recruitment	24 October 2017
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	Spain: 6
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Estonia: 15
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Latvia: 13

Country: Number of subjects enrolled	Georgia: 19
Country: Number of subjects enrolled	Russian Federation: 51
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	Ukraine: 31
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Philippines: 73
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	300
EEA total number of subjects	96

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)	123
From 65 to 84 years	160
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

A total of 123 sites were opened for enrollment.

Pre-assignment

Screening details:

Male or female subjects 18 years of age or older who had a documented nosocomial pneumonia (HABP/VABP/HCABP) caused by an aerobic Gram-negative pathogen only and all must have Gram-negative infection involving the lower respiratory tract.

Pre-assignment period milestones

Number of subjects started	300
Number of subjects completed	300

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, Assessor

Blinding implementation details:

Cefiderocol was prepared and administered within the same time frame after preparation as meropenem. The infusion bag containing a reconstituted study or comparator drug was identified with the study number and subject's identification number but did not identify the specific drug product. For comparability of cefiderocol and the comparator drug meropenem, the dosing solutions were normal saline and were both dosed 2 g, administered IV over 3 hours, q8h (for patients with normal renal function).

Arms

Are arms mutually exclusive?	Yes
Arm title	Cefiderocol

Arm description:

Cefiderocol (1 g/vial) was provided as a powder for solution for IV administration

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:

The proposed cefiderocol dosage regimen for the treatment of serious or life-threatening infections is 2 g q8h infused over 3 hours.

The initial dosage for each subject was adjusted based on eGFR calculated by MDRD equation and CrCl by Cockcroft-Gault equation.

Renal function for all subjects was assessed at early assessment (EA) to determine whether there were changes in renal function for which the dosage of the study treatment needed to be adjusted. The main purpose for this was to ensure that drug levels remained in a safe and therapeutic range. If renal function was changed at EA from Screening, dose adjustment was required.

For subjects with eGFR ≥ 90 mL/min/1.73 m² and CrCl ≥ 120 mL/min by Cockcroft Gault equation at Screening or at EA, a CrCl measured by urinary excretion with urine collection of 2 hours to 8 hours duration was determined in order to determine whether an additional dose adjustment was required.

Arm title	meropenem
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Arm description:

A powder for solution for injection or infusion, as commercially available, 500/1000 mg/vial)

Arm type	Active comparator
Investigational medicinal product name	meropenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dosage for meropenem of 2 g q8h with infusion over 3 hours.

Number of subjects in period 1	Cefiderocol	meropenem
Started	148	152
Completed	106	110
Not completed	42	42
Adverse event, serious fatal	39	34
Recovery	-	1
Adverse event, non-fatal	-	1
other	-	3
Lack of efficacy	1	-
Withdrawal by subject	2	3

Baseline characteristics

Reporting groups

Reporting group title	Cefiderocol
Reporting group description: Cefiderocol (1 g/vial) was provided as a powder for solution for IV administration	
Reporting group title	meropenem
Reporting group description: A powder for solution for injection or infusion, as commercially available, 500/1000 mg/vial)	

Reporting group values	Cefiderocol	meropenem	Total
Number of subjects	148	152	300
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)	65	58	123
65 years or more	83	94	177
Gender categorical Units: Subjects			
Female	47	46	93
Male	101	106	207

Subject analysis sets

Subject analysis set title	Modified Intent-to-Treat cefiderocol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified Intent-to-Treat (mITT) population: All subjects in the ITT population who had evidence of a Gram-negative infection of the lower respiratory tract based on either a culture, Gram stain, or other diagnostic test OR who had evidence of a lower respiratory infection, but culture or other diagnostic tests did not provide a microbiological diagnosis	
Subject analysis set title	Modified Intent-to-Treat meropenem
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified Intent-to-Treat (mITT) population: All subjects in the ITT population who had evidence of a Gram-negative infection of the lower respiratory tract based on either a culture, Gram stain, or other diagnostic test OR who had evidence of a lower respiratory infection, but culture or other diagnostic tests did not provide a microbiological diagnosis	
Subject analysis set title	Safety population cefiderocol
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population: All randomized subjects who received at least 1 dose of the study treatment (identical to the ITT population)	
Subject analysis set title	Safety population meropenem

Subject analysis set type	Safety analysis
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Subject analysis set description:

- Safety population: All randomized subjects who received at least 1 dose of the study treatment (identical to the ITT population)

Reporting group values	Modified Intent-to-Treat cefiderocol	Modified Intent-to-Treat meropenem	Safety population cefiderocol
Number of subjects	145	147	148
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)	65	58	65
65 years or more	80	89	83
Gender categorical			
Units: Subjects			
Female	46	46	47
Male	99	101	101

Reporting group values	Safety population meropenem		
Number of subjects	150		
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		
Adults (18-64 years)	58		
65 years or more	92		
Gender categorical			
Units: Subjects			
Female	46		
Male	104		

End points

End points reporting groups

Reporting group title	Cefiderocol
Reporting group description: Cefiderocol (1 g/vial) was provided as a powder for solution for IV administration	
Reporting group title	meropenem
Reporting group description: A powder for solution for injection or infusion, as commercially available, 500/1000 mg/vial)	
Subject analysis set title	Modified Intent-to-Treat cefiderocol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified Intent-to-Treat (mITT) population: All subjects in the ITT population who had evidence of a Gram-negative infection of the lower respiratory tract based on either a culture, Gram stain, or other diagnostic test OR who had evidence of a lower respiratory infection, but culture or other diagnostic tests did not provide a microbiological diagnosis	
Subject analysis set title	Modified Intent-to-Treat meropenem
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified Intent-to-Treat (mITT) population: All subjects in the ITT population who had evidence of a Gram-negative infection of the lower respiratory tract based on either a culture, Gram stain, or other diagnostic test OR who had evidence of a lower respiratory infection, but culture or other diagnostic tests did not provide a microbiological diagnosis	
Subject analysis set title	Safety population cefiderocol
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population: All randomized subjects who received at least 1 dose of the study treatment (identical to the ITT population)	
Subject analysis set title	Safety population meropenem
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population: All randomized subjects who received at least 1 dose of the study treatment (identical to the ITT population)	

Primary: Primary: All-Cause Mortality Rate at Day 14 (Modified Intent-to-Treat Population)

End point title	Primary: All-Cause Mortality Rate at Day 14 (Modified Intent-to-Treat Population)
End point description: The study hypothesis was that the all-cause mortality rate at Day 14 in subjects who received cefiderocol would be noninferior to that in subjects who received high-dose meropenem. The margin of noninferiority was 12.5%.	
End point type	Primary
End point timeframe: The primary efficacy endpoint was all-cause mortality at Day 14 since the first infusion of study treatment. All-cause mortality rate at Day 14 were calculated as the proportion of subjects in each treatment group who experienced mortality	

End point values	Modified Intent-to-Treat cefiderocol	Modified Intent-to-Treat meropenem		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	145	147		
Units: 292				
All Cause mortality at Day 14	18	17		

Statistical analyses

Statistical analysis title	Cefiderocol vs meropenem
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Statistical analysis description:

Adjusted estimates of the difference in the all-cause mortality at Day 14 between cefiderocol and meropenem groups were calculated along with 95% confidence intervals (CIs) based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights, which were calculated with APACHE II score (≤ 15 and ≥ 16) as the stratified factor. The CIs were 2-sided. Noninferiority (NI) was concluded if the upper bound of 95% CI for the difference in mortality at Day 14 was less than NI margin of 12.5%

Comparison groups	Modified Intent-to-Treat meropenem v Modified Intent-to-Treat cefiderocol
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.002 ^[1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	8.2
Variability estimate	Standard deviation

Notes:

[1] - p-value for noninferiority hypothesis.

Secondary: Secondary: All-Cause Mortality Rate at Day 14 Excluding Subjects Who Were Meropenem Resistant (Supplementary Analysis) (Modified Intent-to-Treat Population)

End point title	Secondary: All-Cause Mortality Rate at Day 14 Excluding Subjects Who Were Meropenem Resistant (Supplementary Analysis) (Modified Intent-to-Treat Population)
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End point description:

A supplementary analysis of the primary endpoint in which subjects who were resistant to meropenem at baseline based on CLSI susceptibility results

End point type	Secondary
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End point timeframe:

Day 14

End point values	Cefiderocol	meropenem	Modified Intent-to-Treat cefiderocol	Modified Intent-to-Treat meropenem
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	148	150	145	147
Units: 292	145	147	9	10

Statistical analyses

Statistical analysis title	Cefiderocol vs meropenem
Statistical analysis description: A supplementary analysis of the primary endpoint in which subjects who were resistant to meropenem at baseline based on CLSI susceptibility	
Comparison groups	Cefiderocol v meropenem
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	other ^[2]
Parameter estimate	Mean difference (final values)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	7.5
Variability estimate	Standard deviation

Notes:

[2] - Sensitivity analysis

Secondary: Secondary: Clinical Outcome at TOC

End point title	Secondary: Clinical Outcome at TOC
End point description: The clinical response rate at EA, EOT, and TOC (as defined in Section 9.5.1.1.2 was calculated as the proportion of subjects in each treatment group who had a clinical outcome of cure at TOC.	
End point type	Secondary
End point timeframe: early assessment, end of trial, test-of-cure	

End point values	Modified Intent-to-Treat cefiderocol	Modified Intent-to-Treat meropenem		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	145	147		
Units: 292				
Clinical cure	94	98		
Clinical failure	27	31		
Indeterminate	24	18		

Statistical analyses

Statistical analysis title	Cefiderocol vs meropenem
Statistical analysis description: The clinical response rate at TOC was calculated as the proportion of subjects in each treatment group who had a clinical outcome of cure at TOC. The adjusted estimate of the difference in the cure rate between the 2 treatment groups was tabulated along with the adjusted 95% CIs based on the CMH weights (diagnosis and APACHE II score). In addition, the number and proportion of subjects having a clinical outcome of failure and indeterminate were summarized by treatment group	
Comparison groups	Modified Intent-to-Treat meropenem v Modified Intent-to-Treat cefiderocol
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.5
upper limit	8.5
Variability estimate	Standard deviation

Secondary: Microbiological outcome at TOC

End point title	Microbiological outcome at TOC
End point description: The microbiological response rate at EA, EOT, and TOC was calculated as the proportion of subjects in each treatment group who experienced eradication at each time point by treatment group.	
End point type	Secondary
End point timeframe: early assessment, end of trial and test-of-cure	

End point values	Modified Intent-to-Treat cefiderocol	Modified Intent-to-Treat meropenem		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	145	147		
Units: 292				
Test of cure	124	127		
Eradication	59	61		

Persistence	26	27		
Indeterminate	39	39		

Statistical analyses

Statistical analysis title	Cefiderocol vs meropenem
Statistical analysis description:	
The adjusted estimate of the difference in the response rate between the 2 treatment groups was tabulated along with the 95% CIs based on a stratified analysis using the CMH weights: infection diagnosis and APACHE score (≤ 15 and ≥ 16). (HABP/VABP/HCABP) and APACHE II score (≤ 15 and ≥ 16). In addition, the number and proportion of subjects having microbiological outcome as persistence and indeterminate were summarized by treatment group.	
Comparison groups	Modified Intent-to-Treat cefiderocol v Modified Intent-to-Treat meropenem
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	10.7
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from the time of having signed ICF through approximately 28 days after the last dose of study treatment for randomized subjects. If a subject withdrew early from the study, AEs collected for 28 days after last dose of treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	cefiderocol
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Reporting group description: -	
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Reporting group title	meropenem
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Reporting group description: -	
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Serious adverse events	cefiderocol	meropenem	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 148 (36.49%)	45 / 150 (30.00%)	
number of deaths (all causes)	39	35	
number of deaths resulting from adverse events	39	35	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer metastatic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 148 (0.68%)	5 / 150 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 5	
Vascular disorders			
Femoral artery embolism			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypovolaemic shock			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Leg amputation			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (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			
Death			
subjects affected / exposed	1 / 148 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
General physical health deterioration			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 148 (2.70%)	4 / 150 (2.67%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 4	1 / 4	

Sudden death			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Pleural effusion			
subjects affected / exposed	1 / 148 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	6 / 148 (4.05%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Bronchopleural fistula			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	3 / 148 (2.03%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	3 / 148 (2.03%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pulmonary congestion			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 148 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 148 (1.35%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			

subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 148 (1.35%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Stridor			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (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	1 / 148 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 148 (0.68%)	5 / 150 (3.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver function test abnormal			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			

subjects affected / exposed	2 / 148 (1.35%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 148 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Splenic rupture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 148 (1.35%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	7 / 148 (4.73%)	5 / 150 (3.33%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 5	0 / 4	
Cardiac failure			
subjects affected / exposed	2 / 148 (1.35%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cardiac failure acute			
subjects affected / exposed	0 / 148 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	

Cardiac failure congestive subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest subjects affected / exposed	3 / 148 (2.03%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiogenic shock subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular disorder subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular insufficiency subjects affected / exposed	1 / 148 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Left ventricular dysfunction subjects affected / exposed	2 / 148 (1.35%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			

Autonomic nervous system imbalance			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain injury			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 148 (1.35%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	2 / 148 (1.35%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lacunar stroke			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			

subjects affected / exposed	1 / 148 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 148 (0.68%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
haemorrhagic anaemia			
subjects affected / exposed	0 / 148 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 148 (0.68%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute abdomen			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal infarction			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			

Diabetic foot			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (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	1 / 148 (0.68%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Meningitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis bacterial			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 148 (4.05%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 2	
Pneumonia bacterial			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia necrotising			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomonas infection			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis			
subjects affected / exposed	3 / 148 (2.03%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	1 / 3	0 / 2	
Septic encephalopathy			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	4 / 148 (2.70%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Spinal cord infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lactic acidosis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	cefiderocol	meropenem	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	130 / 148 (87.84%)	129 / 150 (86.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 148 (6.08%)	6 / 150 (4.00%)	
occurrences (all)	9	6	
Hepatic enzyme increased			
subjects affected / exposed	4 / 148 (2.70%)	10 / 150 (6.67%)	
occurrences (all)	4	10	
Injury, poisoning and procedural complications			
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 148 (6.76%)	6 / 150 (4.00%)	
occurrences (all)	10	6	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 148 (1.35%)	10 / 150 (6.67%)	
occurrences (all)	2	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 148 (8.11%)	12 / 150 (8.00%)	
occurrences (all)	12	12	
Thrombocytopenia			
subjects affected / exposed	2 / 148 (1.35%)	8 / 150 (5.33%)	
occurrences (all)	2	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 148 (8.78%)	13 / 150 (8.67%)	
occurrences (all)	13	13	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	10 / 148 (6.76%)	6 / 150 (4.00%)	
occurrences (all)	10	6	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	4 / 148 (2.70%)	10 / 150 (6.67%)	
occurrences (all)	4	10	

Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	11 / 148 (7.43%) 11 23 / 148 (15.54%) 23	8 / 150 (5.33%) 8 16 / 150 (10.67%) 16	
Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all)	5 / 148 (3.38%) 5 16 / 148 (10.81%) 16 8 / 148 (5.41%) 8 4 / 148 (2.70%) 4	8 / 150 (5.33%) 8 23 / 150 (15.33%) 23 1 / 150 (0.67%) 1 10 / 150 (6.67%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2016	added a repeat of PK blood sampling in the event that the study dosage was changed due to changes in renal function at EA; added the topline results of the thorough QT (TQT) study, which demonstrated that cefiderocol had no clinically significant effect of regulatory concern on the QTc interval and removed the requirement for ECG evaluations other than at Screening based on the results of the TQT study; updated the status of the then ongoing cUTI Study and the DSMB review process/results; added the requirement for a Day 14 and Day 28 survival assessment if these study days for an individual subject did not already have assigned study procedures; and provided editorial/administrative changes and clarifications.
24 July 2017	clarified that linezolid administration is mandated only for at least 5 days (ie, added criteria under which linezolid could be discontinued after 5 days); added valproic acid to the list of prohibited concomitant therapy; added an additional DSMB meeting after 150 subjects were enrolled to re-estimate the necessary sample size; provided the option to raise the minimum APACHE II score to ≥ 8 if the mortality rate was deemed insufficient after 50 subjects had completed the study; excluded subjects with lung abscess or clinical bronchiectasis; added rescreeing criteria; clarified process for reporting SAEs; and provided editorial/administrative changes and clarifications
21 December 2018	revised the address for the location of the Shionogi office responsible for European study sites from London to Amsterdam to a European country-specific amendment
22 February 2019	revised the address for the Shionogi office responsible for European/Middle Eastern study sites from London to Amsterdam for the global protocol; added the Russia-specific change in absolute nucleophil count to the global protocol; added the statistical analysis of superiority for all-cause mortality at Day 14 to the list of key secondary endpoints and provided criteria for concluding superiority; clarified that analysis of the pharmacoeconomic endpoint (resource utilization) would be done outside the CSR; clarified the use of antibiotics for infections other than Gram negative pneumonia (anaerobic or C. difficile infections); added the requirement that carbapenem resistance status of isolated pathogens be recorded in the eCRF; clarified that analyses performed by the DSMB, which were blinded to the sponsor's personnel and not shared with the sponsor, were considered interim analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported