Clinical trial results:
A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Estimate the Efficacy and Safety of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem/Cilastatin in Subjects with Imipenem-Resistant Bacterial Infection

Summary

EudraCT number	2015-000066-62
Trial protocol	DE EE LV RO LT GR IT Outside EU/EEA
Global end of trial date	18 September 2017

Results information

Result version number	v1 (current)
This version publication date	22 September 2018
First version publication date	22 September 2018

Trial information

Trial identification

Sponsor protocol code	7655A-013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02452047
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC-CTI: 163367

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Senior Vice President, Global Clinical Development, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Senior Vice President, Global Clinical Development, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001809-PIP01-15
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	18 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study will evaluate the efficacy and safety of imipenem+cilastatin/relebactam (MK-7655A) versus colistimethate sodium+imipenem+cilastatin in the treatment of imipenem-resistant bacterial infections. Infections evaluated in the study will be hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), complicated intra-abdominal infection (cIAI), and complicated urinary tract infection (cUTI).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Ukraine: 19
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	50
EEA total number of subjects	13

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)	28
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 35 study centers in 17 countries.

Pre-assignment

Screening details:

Adult participants with hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), complicated intra-abdominal infection (cIAI), or complicated urinary tract infection (cUTI) were recruited.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Imipenem+Cilastatin/Relebactam

Arm description:

Participants with HABP, VABP, cIAI, or cUTI caused by imipenem-nonsusceptible but imipenem/relebactam- and colistin-susceptible pathogens were randomized to receive imipenem+cilastatin/relebactam IV infusion once every 6 hours and placebo for colistimethate sodium IV infusion once every 12 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).

Arm type	Experimental
Investigational medicinal product name	Imipenem+Cilastatin/Relebactam
Investigational medicinal product code	
Other name	MK-7655A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imipenem+Cilastatin/Relebactam 200/100 mg to 500/250 mg, depending on renal function, IV infusion once every 6 hours

Investigational medicinal product name	Placebo to Colistimethate sodium (CMS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to CMS IV infusion once every 12 hours

Arm title	Group 2: Colistimethate sodium + Imipenem+Cilastatin

Arm description:

Participants with HABP, VABP, cIAI, or cUTI caused by imipenem-nonsusceptible but imipenem/relebactam- and colistin-susceptible pathogens were randomized to receive colistimethate sodium IV infusion once every 12 hours and imipenem+cilastatin IV infusion once every 6 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).

Arm type	Active comparator

Investigational medicinal product name	CMS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Colistimethate base activity 300 mg (~720 mg CMS or ~9 million IU) IV infusion loading dose, followed by colistimethate base activity 75 mg to 150 mg (~180 to 360 mg CMS), depending on renal function, once every 12 hours

Investigational medicinal product name	Imipenem+Cilastatin/Relebactam
Investigational medicinal product code	
Other name	MK-7655A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imipenem+Cilastatin/Relebactam 200/100 mg to 500/250 mg, depending on renal function, IV infusion once every 6 hours

Arm title	Group 3: Open-Label Imipenem+Cilastatin/Relebactam

Arm description:

Participants with HABP, VABP, cIAI, or cUTI caused by imipenem- and colistin-nonsusceptible pathogens received open-label imipenem+cilastatin/relebactam IV infusion once every 6 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).

Arm type	Experimental
Investigational medicinal product name	Imipenem+Cilastatin/Relebactam
Investigational medicinal product code	
Other name	MK-7655A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imipenem+Cilastatin/Relebactam 200/100 mg to 500/250 mg, depending on renal function, IV infusion once every 6 hours

Number of subjects in period 1	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam
Started	31	16	3
Completed	27	11	1
Not completed	4	5	2
Physician decision	1	-	-
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	1	1
Death	1	3	1
Lost to follow-up	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: Imipenem+Cilastatin/Relebactam
Reporting group description:	
Participants with HABP, VABP, cIAI, or cUTI caused by imipenem-nonsusceptible but imipenem/relebactam- and colistin-susceptible pathogens were randomized to receive imipenem+cilastatin/relebactam IV infusion once every 6 hours and placebo for colistimethate sodium IV infusion once every 12 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).	
Reporting group title	Group 2: Colistimethate sodium + Imipenem+Cilastatin
Reporting group description:	
Participants with HABP, VABP, cIAI, or cUTI caused by imipenem-nonsusceptible but imipenem/relebactam- and colistin-susceptible pathogens were randomized to receive colistimethate sodium IV infusion once every 12 hours and imipenem+cilastatin IV infusion once every 6 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).	
Reporting group title	Group 3: Open-Label Imipenem+Cilastatin/Relebactam
Reporting group description:	
Participants with HABP, VABP, cIAI, or cUTI caused by imipenem- and colistin-nonsusceptible pathogens received open-label imipenem+cilastatin/relebactam IV infusion once every 6 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).	

Reporting group values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam
Number of subjects	31	16	3
Age categorical Units: Subjects			
Adults (18-64 years)	19	7	2
From 65-84 years	12	9	1
Age Continuous Units: Years			
arithmetic mean	56.1	62.8	50.0
standard deviation	± 16.5	± 14.9	± 23.1
Sex: Female, Male Units: Subjects			
Female	11	6	2
Male	20	10	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	0
White	26	15	3
More than one race	4	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	50		

Age categorical Units: Subjects			
Adults (18-64 years)	28		
From 65-84 years	22		
Age Continuous Units: Years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Subjects			
Female	19		
Male	31		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	44		
More than one race	4		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Group 1: Imipenem+Cilastatin/Relebactam
Reporting group description:	
Participants with HABP, VABP, cIAI, or cUTI caused by imipenem-nonsusceptible but imipenem/relebactam- and colistin-susceptible pathogens were randomized to receive imipenem+cilastatin/relebactam IV infusion once every 6 hours and placebo for colistimethate sodium IV infusion once every 12 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).	
Reporting group title	Group 2: Colistimethate sodium + Imipenem+Cilastatin
Reporting group description:	
Participants with HABP, VABP, cIAI, or cUTI caused by imipenem-nonsusceptible but imipenem/relebactam- and colistin-susceptible pathogens were randomized to receive colistimethate sodium IV infusion once every 12 hours and imipenem+cilastatin IV infusion once every 6 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).	
Reporting group title	Group 3: Open-Label Imipenem+Cilastatin/Relebactam
Reporting group description:	
Participants with HABP, VABP, cIAI, or cUTI caused by imipenem- and colistin-nonsusceptible pathogens received open-label imipenem+cilastatin/relebactam IV infusion once every 6 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).	

Primary: Percentage of Participants with Favorable Overall Response (FOR)

End point title	Percentage of Participants with Favorable Overall Response (FOR)
End point description:	
FOR criteria was based on clinically relevant outcomes for the primary infection site as follows: HABP/VABP: survival through Day 28; cIAI: favorable clinical response (all pretherapy symptoms of index infection resolved with no evidence of resurgence, no additional antibiotic therapy required, and no unplanned surgical or percutaneous drainage procedures) at Day 28; cUTI: favorable composite clinical response (all pretherapy symptoms of index infection resolved with no evidence of resurgence, no additional antibiotic therapy required) and microbiological response (urine culture shows sustained eradication of the baseline uropathogen [e.g., ≥10^5 CFU/mL at study entry is reduced to <10^4 CFU/mL]) at Early Follow-up (EFU). Participants in Groups 1 and 2 who received ≥1 dose of each trial drug within an IV regimen, and had a baseline bacterial pathogen meeting inclusion criteria, are included. Per protocol, data from Group 3 was considered exploratory and not included in the analysis.	
End point type	Primary
End point timeframe:	
Up to Day 30 (up to 9 days after completing study treatment)	

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	10	0[1]	
Units: Percentage of Participants				
number (confidence interval 95%)	71.4 (49.8 to 86.4)	70.0 (39.2 to 89.7)	(to)	

Notes:

[1] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Adjusted difference in FOR %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FOR %
Point estimate	-7.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-27.5
upper limit	21.4

Primary: Percentage of Participants with ≥1 Adverse Events (AEs)

End point title	Percentage of Participants with ≥1 Adverse Events (AEs)

End point description:

The percentage of participants in Groups 1, 2, and 3 experiencing ≥1 AEs during treatment and 14-day follow-up was determined. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Statistical analysis included only Groups 1 and 2 as indicated by the protocol. All participants in Groups 1, 2, and 3 who received ≥1 dose of study drug are included.

End point type	Primary

End point timeframe:

Up to Day 35 (up to 14 days after completing study treatment)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	3	
Units: Percentage of Participants				
number (not applicable)	71.0	81.3	100.0	

Statistical analyses

Statistical analysis title	Difference in AE %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in AE %
Point estimate	-10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.1
upper limit	18

Primary: Percentage of Participants with ≥1 Serious Adverse Events (SAEs)

End point title	Percentage of Participants with ≥1 Serious Adverse Events (SAEs)

End point description:

The percentage of participants in Groups 1, 2, and 3 experiencing ≥1 SAEs during treatment and 14-day follow-up was determined. An SAE is any untoward medical occurrence that, at any dose, results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant injury/incapacity; is a congenital anomaly/birth defect; or is an other important medical event. Statistical analysis included only Groups 1 and 2. All participants in Groups 1, 2, and 3 who received ≥1 dose of study drug are included.

End point type	Primary

End point timeframe:

Up to Day 35 (up to 14 days after completing study treatment)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	3	
Units: Percentage of Participants				
number (not applicable)	9.7	31.3	100.0	

Statistical analyses

Statistical analysis title	Difference in SAE %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in SAE %
Point estimate	-21.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.8
upper limit	1.3

Primary: Percentage of Participants with ≥1 Drug-Related AEs

End point title	Percentage of Participants with ≥1 Drug-Related AEs

End point description:

The percentage of participants in Groups 1, 2, and 3 experiencing ≥1 drug-related AEs during treatment and 14-day follow-up was determined. A drug-related AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, and considered by the investigator to be related to the study intervention. Statistical analysis included only Groups 1 and 2. All participants in Groups 1, 2, and 3 who received ≥1 dose of study drug are included.

End point type	Primary

End point timeframe:

Up to Day 35 (up to 14 days after completing study treatment)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	3	
Units: Percentage of Participants				
number (not applicable)	16.1	31.3	33.3	

Statistical analyses

Statistical analysis title	Difference in drug-related AE %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in drug-related AE %
Point estimate	-15.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.3
upper limit	9.2

Primary: Percentage of Participants with ≥1 Drug-Related SAEs

End point title	Percentage of Participants with ≥1 Drug-Related SAEs

End point description:

The percentage of participants in Groups 1, 2, and 3 experiencing ≥1 drug-related SAEs during treatment and 14-day follow-up was determined. A drug-related SAE is any untoward medical occurrence that, at any dose, results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant injury/incapacity; is a congenital anomaly/birth defect; or is an other important medical event, that is considered by the investigator to be related to the study intervention. Statistical analysis included only Groups 1 and 2 as indicated by the protocol. All participants in Groups 1, 2, and 3 who received ≥1 dose of study drug are included.

End point type	Primary

End point timeframe:

Up to Day 35 (up to 14 days after completing study treatment)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	3	
Units: Percentage of Participants				
number (not applicable)	0.0	0.0	33.3	

Statistical analyses

Statistical analysis title	Difference in drug-related SAE %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in drug-related SAE %
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7
upper limit	11.2

Primary: Percentage of Participants Discontinuing from Study Therapy due to ≥1 AEs

End point title	Percentage of Participants Discontinuing from Study Therapy due to ≥1 AEs

End point description:

The percentage of participants in Groups 1, 2, and 3 discontinuing from study drug due to ≥1 AEs during the treatment period was determined. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Statistical analysis included only Groups 1 and 2 as indicated by the protocol. All participants in Groups 1, 2, and 3 who received ≥1 dose of study drug are included.

End point type	Primary

End point timeframe:

Up to Day 21

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	3	
Units: Percentage of Participants				
number (not applicable)	0.0	18.8	33.3	

Statistical analyses

Statistical analysis title	Difference in discontinuation %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in discontinuation %
Point estimate	-18.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.3
upper limit	-6.2

Primary: Percentage of Participants Discontinuing from Study Therapy due to ≥1 Drug-Related AEs

End point title	Percentage of Participants Discontinuing from Study Therapy due to ≥1 Drug-Related AEs

End point description:

The percentage of participants in Groups 1, 2, and 3 discontinuing from study drug due to ≥1 drug-related AEs during the treatment period was determined. A drug-related AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, and considered by the investigator to be related to the study intervention. Statistical analysis included only Groups 1 and 2 as indicated by the protocol. All participants in Groups 1, 2, and 3 who received ≥1 dose of study drug are included.

End point type	Primary

End point timeframe:

Up to Day 21

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	3	
Units: Percentage of Participants				
number (not applicable)	0.0	12.5	33.3	

Statistical analyses

Statistical analysis title	Difference in drug-related discontinuation %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in drug-related discon %
Point estimate	-12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.3
upper limit	-0.3

Primary: Analysis of Specific AEs with an Incidence of ≥4 Participants in a Treatment Group

End point title	Analysis of Specific AEs with an Incidence of ≥4 Participants in a Treatment Group

End point description:

The number of participants experiencing AEs that occurred in ≥4 participants within either Group 1 or Group 2 was assessed. An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. All participants in Groups 1 and 2 who received ≥1 dose of study drug are included; Group 3 had <4 participants and therefore no data are presented.

End point type	Primary

End point timeframe:

Up to Day 35 (up to 14 days after completing study treatment)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	0[2]	
Units: Percentage of Participants				
number (not applicable)				
Pyrexia|	12.9	12.5		
Blood creatinine increased|	0.0	25.0		

Notes:

[2] - Group 3 had <4 participants and therefore no data are presented.

Statistical analyses

Statistical analysis title	Difference in pyrexia %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in pyrexia %
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.2
upper limit	19.7

Statistical analysis title	Difference blood creatinine increased %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference blood creatinine inc %
Point estimate	-25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.8
upper limit	-10.1

Primary: Percentage of Participants with ≥1 Events of Clinical Interest (ECI)

End point title	Percentage of Participants with ≥1 Events of Clinical Interest (ECI)

End point description:

The percentage of participants in Groups 1, 2, and 3 with ECIs within 2 categories was determined. Category 1 ECIs included post-baseline laboratory values of an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value that is ≥3x upper limit of normal (ULN) and an elevated total bilirubin value that is ≥2x ULN and (at the same time) an alkaline phosphatase value that is ≤2x ULN. Category 2 ECIs included a confirmed elevated AST or ALT value that is ≥5x ULN. Statistical analysis includes on Groups 1 and 2 as indicated by the protocol. All participants in Groups 1, 2 and 3 who received ≥1 dose of study drug are included.

End point type	Primary

End point timeframe:

Up to Day 35 (up to 14 days after completing study treatment)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	3	
Units: Percentage of Participants				
number (not applicable)				
Category 1 ECI	0.0	12.5	0.0	
Category 2 ECI	0.0	12.5	0.0	

Statistical analyses

Statistical analysis title	Difference in Category 1 ECI %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Difference in Category 1 ECI %
Point estimate	-12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.3
upper limit	-0.3

Notes:

[3] - Difference in percentages

Statistical analysis title	Difference in Category 2 ECI

Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Difference in Category 2 ECI %
Point estimate	-12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.3
upper limit	-0.3

Notes:

[4] - Difference in percentages

Secondary: Percentage of Participants with ≥1 Events of Treatment-Emergent Nephrotoxicity

End point title	Percentage of Participants with ≥1 Events of Treatment-Emergent Nephrotoxicity

End point description:

Treatment-emergent nephrotoxity was assessed in Groups 1 and 2 as indicated by the protocol (Group 3 was not included). Nephrotoxicity for participants with normal baseline serum creatinine levels (<1.2 mg/dL) was defined as "doubling of serum creatinine to >1.2 mg/dL or reduction in creatinine clearance (ClCR) of ≥50%". Nephrotoxicity for participants with pre-existing renal dysfunction (baseline serum creatinine level ≥1.2 mg/dL) was defined as "increase in serum creatinine by ≥1 mg/dL or reduction from baseline ClCR of ≥20% or need for renal replacement therapy (RRT)". All participants in Groups 1 and 2 who received ≥1 dose of study drug are included. Per protocol, Group 3 was not included in the nephrotoxicity analysis.

End point type	Secondary

End point timeframe:

Up to Day 35 (up to 14 days after completing study treatment)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	16	0[5]	
Units: Percentage of Participants				
number (confidence interval 95%)	10.3 (2.8 to 27.2)	56.3 (33.2 to 76.9)	(to)	

Notes:

[5] - Group 3 was not included in the nephrotoxicity analysis.

Statistical analyses

Statistical analysis title	Difference in nephrotoxicity %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002
Method	Fisher exact
Parameter estimate	Difference in nephrotoxicity %
Point estimate	-45.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69.1
upper limit	-18.4

Secondary: Percentage of Participants with Favorable Clinical Response (FCR) at Day 28

End point title	Percentage of Participants with Favorable Clinical Response (FCR) at Day 28

End point description:

FCR was defined as "sustained cure" or "cure". Sustained cure (for participants with "cure" response at prior visit) was defined as "all pretherapy signs and symptoms of index infection resolved with no evidence of resurgence and no additional antibiotic therapy required, and (for cIAI participants) no unplanned surgical procedures or percutaneous drainage procedures have been performed". Cure (for participants with "improved" response at EOT) was defined as "all pretherapy signs and symptoms of index infection resolved or returned to preinfection status, and no additional IV antibiotic therapy required, and (for cIAI participants) no unplanned surgical procedures or percutaneous drainage procedures performed". All participants in Groups 1 and 2 who received ≥1 dose of each trial drug within an IV treatment regimen, and who had a baseline bacterial pathogen meeting inclusion criteria, are included. As per protocol, Group 3 was not included in the comparative analysis.

End point type	Secondary

End point timeframe:

Day 28

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	10	0[6]	
Units: Percentage of Participants				
number (confidence interval 95%)	71.4 (49.8 to 86.4)	40.0 (16.7 to 68.8)	(to)	

Notes:

[6] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Adjusted difference in Day 28 FCR %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Adjusted difference in %
Point estimate	26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	51.5

Notes:

[7] - Adjusted difference and 90% confidence intervals based on the Miettinen & Nurminen method stratified by infection-site stratum.

Secondary: Percentage of Participants with All-cause Mortality Up to Day 28

End point title	Percentage of Participants with All-cause Mortality Up to Day 28

End point description:

The percentage of participants with all-cause mortality up to Day 28 was determined for Groups 1 and 2. All participants in Group 1 and Group 2 who received ≥1 dose of each trial drug within a given IV treatment regimen, and who had a baseline bacterial pathogen that met inclusion criteria, are included. As per protocol, Group 3 was not included in the comparative analysis.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	10	0[8]	
Units: Percentage of Participants				
number (confidence interval 95%)	9.5 (1.4 to 30.1)	30.0 (10.3 to 60.8)	(to)	

Notes:

[8] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Adjusted difference in mortality %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Adjusted difference in mortality %
Point estimate	-17.3

Confidence interval	
level	90 %
sides	2-sided
lower limit	-46.4
upper limit	6.7

Notes:

[9] - Adjusted difference and 90% confidence intervals based on the Miettinen & Nurminen method stratified by infection-site stratum.

Secondary: Percentage of Participants with Favorable Clinical Response (FCR) on Therapy (OTX)

End point title	Percentage of Participants with Favorable Clinical Response (FCR) on Therapy (OTX)

End point description:

The percentage of participants with a FCR at OTX was determined for Groups 1 and 2. FCR at OTX was defined as "improved". Improved was defined as "all or most pretherapy signs and symptoms of index infection have improved or resolved, and (for cIAI participants) no unplanned surgical procedures or percutaneous drainage procedures have been performed. All participants in Group 1 and Group 2 who received ≥1 dose of each trial drug within a given IV treatment regimen, and who had a baseline bacterial pathogen that met inclusion criteria, are included. As per protocol, Group 3 was not included in the comparative analysis.

End point type	Secondary

End point timeframe:

OTX (Day 3)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	10	0[10]	
Units: Percentage of Participants				
number (confidence interval 95%)	81.0 (59.4 to 92.9)	40.0 (16.7 to 68.8)	(to)	

Notes:

[10] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Adjusted difference in OTX FCR %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Adjusted difference in OTX FCR %
Point estimate	33.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	7.4
upper limit	61.1

Notes:

[11] - Adjusted difference and 90% confidence intervals based on the Miettinen & Nurminen method stratified by infection-site stratum.

Secondary: Percentage of Participants with FCR at End of Therapy (EOT)

End point title	Percentage of Participants with FCR at End of Therapy (EOT)

End point description:

The percentage of participants with FCR at EOT was determined for Groups 1 and 2. FCR at EOT was defined as "cure" or "improved". Cure was defined as "all pretherapy signs and symptoms of index infection resolved or returned to preinfection status, and no additional IV antibiotic therapy required, and (for cIAI participants) no unplanned surgical procedures or percutaneous drainage procedures performed". Improved was defined as "all or most pretherapy signs and symptoms of index infection have improved or resolved, and (for cIAI participants) no unplanned surgical procedures or percutaneous drainage procedures have been performed. All participants in Group 1 and Group 2 who received ≥1 dose of each trial drug within a given IV treatment regimen, and who had a baseline bacterial pathogen that met inclusion criteria, are included. As per protocol, Group 3 was not included in the comparative analysis.

End point type	Secondary

End point timeframe:

At EOT (up to Day 21)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	10	0[12]	
Units: Percentage of Participants				
number (confidence interval 95%)	90.5 (69.9 to 98.6)	60.0 (31.2 to 83.3)	(to)	

Notes:

[12] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Adjusted difference in EOT FCR %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Adjusted difference in EOT FCR %
Point estimate	25.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.1
upper limit	53.6

Notes:

[13] - Adjusted difference and 90% confidence intervals based on the Miettinen & Nurminen method stratified by infection-site stratum.

Secondary: Percentage of Participants with FCR at EFU

End point title	Percentage of Participants with FCR at EFU

End point description:

FCR was defined as "sustained cure" or "cure". Sustained cure (for participants with "cure" response at prior visit) was defined as "all pretherapy signs and symptoms of index infection resolved with no evidence of resurgence and no additional antibiotic therapy required, and (for cIAI participants) no unplanned surgical procedures or percutaneous drainage procedures have been performed". Cure (for participants with "improved" response at EOT) was defined as "all pretherapy signs and symptoms of index infection resolved or returned to preinfection status, and no additional IV antibiotic therapy required, and (for cIAI participants) no unplanned surgical procedures or percutaneous drainage procedures performed". All participants in Groups 1 and 2 who received ≥1 dose of each trial drug within an IV treatment regimen, and who had a baseline bacterial pathogen meeting inclusion criteria, are included. As per protocol, Group 3 was not included in the comparative analysis.

End point type	Secondary

End point timeframe:

EFU (Between Day 10 and Day 30 [5 to 9 Days after EOT])

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	10	0[14]	
Units: Percentage of Participants				
number (confidence interval 95%)	81.0 (59.4 to 92.9)	50.0 (23.7 to 76.3)	(to)	

Notes:

[14] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Adjusted difference in EFU FCR %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[15]
Parameter estimate	Adjusted difference in EFU FCR %
Point estimate	24.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.8
upper limit	51.4

Notes:

[15] - Adjusted difference and 90% confidence intervals based on the Miettinen & Nurminen method stratified by infection-site stratum.

Secondary: Percentage of cUTI Participants with Favorable Microbiological Response (FMR) at OTX

End point title	Percentage of cUTI Participants with Favorable Microbiological Response (FMR) at OTX

End point description:

The percentage of participants with FMR at OTX was determined for participants with cUTI in Groups 1 and 2. FMR was defined as "urine culture results at OTX showing eradication (i.e., ≥10^5 colony forming units [CFU]/mL at baseline was reduced to <10^4 CFU/mL at OTX) of the uropathogen". All participants in Group 1 and Group 2 with cUTI who received ≥1 dose of each trial drug within a given IV treatment regimen, and who had a baseline bacterial pathogen that met inclusion criteria, are included. As per protocol, Group 3 was not included in the comparative analysis.

End point type	Secondary

End point timeframe:

OTX (Day 3)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	5	0[16]	
Units: Percentage of Participants				
number (confidence interval 95%)	100.0 (70.0 to 100.0)	100.0 (51.1 to 100.0)	(to)	

Notes:

[16] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Difference in FMR %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in FMR %
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-20.8
upper limit	36.6

Secondary: Percentage of cUTI Participants with FMR at EOT

End point title	Percentage of cUTI Participants with FMR at EOT

End point description:

The percentage of participants with FMR at EOT was determined for participants with cUTI in Groups 1 and 2. FMR was defined as "urine culture results at EOT showing eradication (i.e., ≥10^5 CFU/mL at baseline was reduced to <10^4 CFU/mL at EOT) or sustained eradication (i.e., ≥10^5 CFU/mL at baseline that was reduced to <10^4 CFU/mL previously remained <10^4 CFU/mL at EOT) of the uropathogen". All participants in Group 1 and Group 2 with cUTI who received ≥1 dose of each trial drug within a given IV treatment regimen, and who had a baseline bacterial pathogen that met inclusion criteria, are included. As per protocol, Group 3 was not included in the comparative analysis.

End point type	Secondary

End point timeframe:

At EOT (up to Day 21)

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	5	0[17]	
Units: Percentage of Participants				
number (confidence interval 95%)	100.0 (70.0 to 100.0)	100.0 (51.1 to 100.0)	(to)	

Notes:

[17] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Difference in FMR %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in FMR %
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-20.8
upper limit	36.6

Secondary: Percentage of cUTI Participants with FMR at EFU

End point title	Percentage of cUTI Participants with FMR at EFU

End point description:

The percentage of participants with FMR at EFU was determined for participants with cUTI in Groups 1 and 2. FMR was defined as "urine culture results at EFU showing sustained eradication (i.e., ≥10^5 CFU/mL at baseline that was reduced to <10^4 CFU/mL previously remained <10^4 CFU/mL at EFU) of the uropathogen". All participants in Group 1 and Group 2 with cUTI who received ≥1 dose of each trial drug within a given IV treatment regimen, and who had a baseline bacterial pathogen that met inclusion criteria, are included. As per protocol, Group 3 was not included in the comparative analysis.

End point type	Secondary

End point timeframe:

EFU (Between Day 10 and Day 30 [5 to 9 Days after EOT])

End point values	Group 1: Imipenem+Cilastatin/Relebactam	Group 2: Colistimethate sodium + Imipenem+Cilastatin	Group 3: Open-Label Imipenem+Cilastatin/Relebactam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	5	0[18]	
Units: Percentage of Participants				
number (confidence interval 95%)	72.7 (42.9 to 90.8)	100.0 (51.1 to 100.0)	(to)	

Notes:

[18] - Group 3 was not included in the comparative analysis.

Statistical analyses

Statistical analysis title	Difference in FMR %
Comparison groups	Group 1: Imipenem+Cilastatin/Relebactam v Group 2: Colistimethate sodium + Imipenem+Cilastatin
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in FMR %
Point estimate	-27.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-52.8
upper limit	12.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 35 (up to 14 days after EOT)

Adverse event reporting additional description:

All participants in Groups 1, 2, and 3 who received ≥1 dose of study drug are included. Any event(s) reported to the investigator outside the AE monitoring period are also included.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Group 1: Imipenem+Cilastin/Relebactam

Reporting group description:

Participants with HABP, VABP, cIAI, or cUTI caused by imipenem-nonsusceptible but imipenem/relebactam- and colistin-susceptible pathogens were randomized to receive imipenem+cilastatin/relebactam IV infusion once every 6 hours and placebo for colistimethate sodium IV infusion once every 12 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).

Reporting group title	Group 2: Colistimethate sodim+Imipenem+Cilastin

Reporting group description:

Participants with HABP, VABP, cIAI, or cUTI caused by imipenem-nonsusceptible but imipenem/relebactam- and colistin-susceptible pathogens were randomized to receive colistimethate sodium IV infusion once every 12 hours and imipenem+cilastatin IV infusion once every 6 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).

Reporting group title	Group 3: Open-label Imipenem+Cilastin/Relebactam

Reporting group description:

Participants with HABP, VABP, cIAI, or cUTI caused by imipenem- and colistin-nonsusceptible pathogens received open-label imipenem+cilastatin/relebactam IV infusion once every 6 hours for 5 to 21 days (cIAI and cUTI) or for 7 to 21 days (HABP or VABP).

Serious adverse events	Group 1: Imipenem+Cilastin/ Relebactam	Group 2: Colistimethate sodim+Imipenem+Cilastin	Group 3: Open-label Imipenem+Cilastin/ Relebactam
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 31 (12.90%)	5 / 16 (31.25%)	3 / 3 (100.00%)
number of deaths (all causes)	2	3	1
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Systemic inflammatory response syndrome			

subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Acute abdomen			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic haematoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Escherichia urinary tract infection			

subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	2 / 3 (66.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

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

Non-serious adverse events	Group 1: Imipenem+Cilastin/ Relebactam	Group 2: Colistimethate sodim+Imipenem+Cilastin	Group 3: Open-label Imipenem+Cilastin/ Relebactam
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 31 (48.39%)	13 / 16 (81.25%)	3 / 3 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Infusion site phlebitis			
subjects affected / exposed	1 / 31 (3.23%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Oedema			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			

subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Peripheral swelling			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	4 / 31 (12.90%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	5	2	0
Immune system disorders			
Chronic graft versus host disease in liver			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 31 (9.68%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Epistaxis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Haemoptysis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hydrothorax			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tachypnoea			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Tracheal mass			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Depression			

subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Product issues			
Device dislocation			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Device occlusion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 31 (9.68%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Blood creatinine increased			
subjects affected / exposed	0 / 31 (0.00%)	4 / 16 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Blood potassium decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			

subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Creatinine renal clearance decreased			
subjects affected / exposed	2 / 31 (6.45%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 31 (3.23%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Liver function test increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Biliary anastomosis complication			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Incision site haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Laceration			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Cardiac disorders			

Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Atrial flutter			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Tachyarrhythmia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 31 (0.00%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 16 (6.25%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Leukopenia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Diarrhoea			

subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Gastritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Haematemesis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 31 (0.00%)	2 / 16 (12.50%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Ileus			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Large intestinal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Large intestinal ulcer			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Large intestine perforation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 31 (6.45%)	3 / 16 (18.75%)	0 / 3 (0.00%)
occurrences (all)	2	3	0
Retching			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			

Hepatic artery stenosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hepatic failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Periportal oedema			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Renal cyst			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Anorectal infection bacterial			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Bacteraemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Bacterial abdominal infection			

subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Biliary tract infection bacterial			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Biliary tract infection fungal			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Device related infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Ear infection bacterial			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Ear infection staphylococcal			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Enterococcal infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Peritoneal candidiasis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Peritonitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Respiratory moniliasis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	1	1	0

Serratia infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Stenotrophomonas infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Streptococcal urinary tract infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 16 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 December 2016	Amendment (AM)1: The primary purpose of AM1 was to allow for a potential increase in enrollment.
08 May 2017	AM2: The primary purpose of AM2 was to allow for treatment durations longer than 21 days based on sponsor approval.
11 September 2017	AM3: The primary purposes of Amendment 03 were to add details to the statistical analysis plan for calculation of 90% confidence intervals for between-group differences for the primary and key secondary efficacy endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported