Clinical trial results:
A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Intra-Abdominal Infection [cIAI]

Summary

EudraCT number	2011-005686-20
Trial protocol	DE ES PT GR LT LV EE BG PL
Global end of trial date	11 August 2014

Results information

Result version number	v2 (current)
This version publication date	28 July 2019
First version publication date	01 August 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	7655-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01506271
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2014
Global end of trial reached?	Yes
Global end of trial date	11 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy, safety and tolerability of adding 125 mg or 250 mg doses of MK-7655 (Relebactam) to imipenem/cilastatin in adults 18 years or older with complicated intra-abdominal infection (cIAI). The primary hypothesis is that the relebactam + imipenem/cilastatin treatment regimen is non-inferior to treatment with imipenem/cilastatin alone with respect to the proportion of participants with a favorable clinical response at completion of intravenous (IV) study therapy.

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	31 May 2012
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	Argentina: 3
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Latvia: 27
Country: Number of subjects enrolled	Lithuania: 21
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Peru: 7
Country: Number of subjects enrolled	Romania: 62
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Taiwan: 10

Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Ukraine: 96
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	351
EEA total number of subjects	163

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)	271
From 65 to 84 years	77
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult males or females 18 years old or older, with cIAI requiring treatment with IV antibiotic therapy were enrolled in this trial.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Relebactam 250 mg + IPM/CIL

Arm description:

Relebactam 250 mg and imipenem/cilastatin (IPM/CIL) 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Arm type	Experimental
Investigational medicinal product name	Relebactam
Investigational medicinal product code	
Other name	MK-7655
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Relebactam 250 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Investigational medicinal product name	Imipenem/Cilastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imipenem/Cilastatin (IPM/CIL) 500 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Arm title	Relebactam 125 mg + IPM/CIL

Arm description:

Relebactam 125 mg and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Arm type	Experimental
Investigational medicinal product name	Imipenem/Cilastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imipenem/Cilastatin (IPM/CIL) 500 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Investigational medicinal product name	Relebactam
Investigational medicinal product code	
Other name	MK-7655
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Relebactam 125 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Arm title	Placebo + IPM/CIL

Arm description:

Placebo for relebactam and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Arm type	Placebo
Investigational medicinal product name	Imipenem/Cilastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imipenem/Cilastatin (IPM/CIL) 500 mg was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Investigational medicinal product name	Placebo for relebactam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Normal saline (0.9%) was administered by IV over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Number of subjects in period 1	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL
Started	118	116	117
Treated	117	116	114
Completed	114	109	114
Not completed	4	7	3
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	1	1
Adverse event, non-fatal	-	2	-
Insufficient supply of study drug	1	-	-
Lost to follow-up	-	1	2
Progressive disease	-	1	-
Protocol deviation	3	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Relebactam 250 mg + IPM/CIL
Reporting group description:	
Relebactam 250 mg and imipenem/cilastatin (IPM/CIL) 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.	
Reporting group title	Relebactam 125 mg + IPM/CIL
Reporting group description:	
Relebactam 125 mg and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.	
Reporting group title	Placebo + IPM/CIL
Reporting group description:	
Placebo for relebactam and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.	

Reporting group values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL
Number of subjects	118	116	117
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	48.3	49.8	49.1
standard deviation	± 18.9	± 17.4	± 17.8
Gender categorical			
Units: Subjects			
Female	44	54	51
Male	74	62	66

Reporting group values	Total		
Number of subjects	351		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	149		
Male	202		

End points

End points reporting groups

Reporting group title	Relebactam 250 mg + IPM/CIL

Reporting group description:

Relebactam 250 mg and imipenem/cilastatin (IPM/CIL) 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Reporting group title	Relebactam 125 mg + IPM/CIL

Reporting group description:

Relebactam 125 mg and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Reporting group title	Placebo + IPM/CIL

Reporting group description:

Placebo for relebactam and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Primary: Percentage of participants with a favorable clinical response at completion of IV study therapy

End point title	Percentage of participants with a favorable clinical response at completion of IV study therapy

End point description:

A favorable clinical response is assessed by the clinical investigator as a cure, and is defined as a situation where all or most pre-therapy signs and symptoms of the index infection have resolved, or returned to pre-infection status, and no additional antibiotic therapy is required. The microbiologically evaluable (ME) population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy.

End point type	Primary

End point timeframe:

4 to 14 days post initiation of IV study therapy (up to post-randomization day 14)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81[1]	86[2]	83[3]	
Units: Percentage of Participants				
number (confidence interval 95%)	96.3 (89.6 to 99.2)	98.8 (93.7 to 100)	95.2 (88.1 to 98.7)	

Notes:

[1] - Two participants with indeterminate or missing responses are excluded from the analysis

[2] - One participant with indeterminate or missing responses is excluded from the analysis

[3] - Two participants with indeterminate or missing responses are excluded from the analysis

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without

stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	8.6

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	10.8

Primary: Percentage of participants with an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory values that are greater than or equal to 5X the upper limit of normal (ULN)

End point title	Percentage of participants with an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory values that are greater than or equal to 5X the upper limit of normal (ULN)

End point description:

Pre-specified events of interest were confirmed (i.e., verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 5 X ULN as a result of within-protocol-specific testing or unscheduled testing. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)	1.7	0	1.8	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Percent Difference
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.979
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	4.5

Notes:

[4] - The analysis type is a traditional test for a non-zero difference.

Statistical analysis title	Relebactam 125 mg - Placebo: Percent Difference
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.153
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	1.5

Notes:

[5] - The analysis type is a traditional test for a non-zero difference.

Primary: Percentage of participants with elevated AST or ALT laboratory values that

are greater than or equal to 3X the ULN, as well as elevated total bilirubin greater than or equal to 2X the ULN, and alkaline phosphatase values that are less than 2X the ULN

End point title	Percentage of participants with elevated AST or ALT laboratory values that are greater than or equal to 3X the ULN, as well as elevated total bilirubin greater than or equal to 2X the ULN, and alkaline phosphatase values that are less than 2X the ULN

End point description:

Pre-specified events of interest were confirmed (i.e., verified by repeat testing) elevated AST or ALT laboratory value that is greater than or equal to 3 X ULN, as well as elevated total bilirubin greater than or equal to 2X the ULN, and alkaline phosphatase values that are less than 2X the ULN, as a result of within-protocol-specific testing or unscheduled testing. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)	0.9	0	0	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Percent Difference
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.324
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	4.7

Notes:

[6] - The analysis type is a traditional test for a non-zero difference.

Statistical analysis title	Relebactam 125 mg - Placebo: Percent Difference
Comparison groups	Placebo + IPM/CIL v Relebactam 125 mg + IPM/CIL

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	> 0.999
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	3.2

Notes:

[7] - The analysis type is a traditional test for a non-zero difference.

Primary: Percentage of participants with any adverse event (AE)

End point title	Percentage of participants with any adverse event (AE)

End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)	48.7	47.4	41.2	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	20.1

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	18.8

Primary: Percentage of participants with any serious adverse event (SAE)

End point title	Percentage of participants with any serious adverse event (SAE)

End point description:

A SAE is any AE occurring at any dose that is life threatening; results in a persistent or significant disability/incapacity; prolongs an existing inpatient hospitalization; is a congenital anomaly/birth defect; or results in death. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)	3.4	9.5	7	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	2.4

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	10.1

Primary: Percentage of participants with any drug-related AE

End point title	Percentage of participants with any drug-related AE

End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. A drug-related AE is an AE determined by the investigator to be possibly, probably or definitely related to drug treatment. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)	13.7	13.8	9.6	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	12.7

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	12.8

Primary: Percentage of participants with any serious drug-related AE

End point title	Percentage of participants with any serious drug-related AE

End point description:

A SAE is any AE occurring at any dose that is life threatening; results in a persistent or significant disability/incapacity; prolongs an existing inpatient hospitalization; is a congenital anomaly/birth defect; or results in death. A drug-related SAE is a SAE determined by the investigator to be possibly, probably or definitely related to drug treatment. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 42 days following completion of all study therapy (up to Day 56)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)	0.9	0	0.9	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	3.9

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	2.4

Primary: Percentage of participants who discontinued IV study therapy due to an AE

End point title	Percentage of participants who discontinued IV study therapy due to an AE

End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. AEs assessed by the investigator that caused discontinuation of participant treatment are presented. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days post initiation of IV study therapy

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)	0.9	4.3	2.6	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	2.3

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	7.4

Primary: Percentage of participants who discontinued IV study therapy due to a drug-related AE

End point title	Percentage of participants who discontinued IV study therapy due to a drug-related AE

End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or

intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. A drug-related AE is an AE determined by the investigator to be possibly, probably or definitely related to drug treatment. Drug-related AEs assessed by the investigator that caused discontinuation of participant treatment are presented. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days post initiation of IV study therapy

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)	0	0.9	2.6	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	0.6

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	2.4

Primary: Percentage of participants with AEs with incidence of >= 4 participants in one treatment group

End point title	Percentage of participants with AEs with incidence of >= 4 participants in one treatment group

End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the medicinal product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the medicinal product, is also an AE. AE preferred terms with incidence greater than or equal to 4 in one treatment group are presented. AEs preferred terms which did not achieve this threshold are not reported. AE preferred terms are based on MedDRA version 17.0. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days post initiation of IV study therapy (up to Day 28)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)				
Diarrhoea	6	6	4.4	
Nausea	6.8	7.8	7	
Vomiting	6	7.8	2.6	
Post-operative wound infection	2.6	1.7	4.4	
Seroma	0.9	4.3	0	
ALT increased	4.3	4.3	3.5	
AST increased	4.3	4.3	2.6	
Lipase increased	2.6	1.7	3.5	
Hypertension	0	2.6	3.5	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Diarrhoea

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	8.1

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Diarrhoea

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Placebo + IPM/CIL v Relebactam 125 mg + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	8.2

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Nausea

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	6.9

Statistical analysis title	Relebactam 125 mg - Placebo: % Difference - Nausea

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	8

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Vomiting

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	9.6

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Vomiting

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	11.8

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Post.inf.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	3.5

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Post.inf.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	2.2

Statistical analysis title	Relebactam 250 mg - Placebo: % Difference - Seroma

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	4.7

Statistical analysis title	Relebactam 125 mg - Placebo: % Difference - Seroma

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	9.7

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - ALT inc.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	6.6

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - ALT inc.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	6.7

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - AST inc.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	7.3

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - AST inc.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Placebo + IPM/CIL v Relebactam 125 mg + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	1.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	7.4

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff.-Lip. inc.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	4.2

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff.-Lip. inc.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	3

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Hyp.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	-0.3

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Hyp.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	4.3

Primary: Percentage of participants with predefined limit of change (PDLC) with incidence of >= 4 participants in one treatment group

End point title	Percentage of participants with predefined limit of change (PDLC) with incidence of >= 4 participants in one treatment group[8]

End point description:

PDLC are presented based on values from the following laboratory tests on serum: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Bil), and alkaline phosphatase (AP). Results are presented for PDLC from tests with reported incidence greater than or equal to 4 participants in one treatment group. Laboratory tests which did not achieve the PDLC threshold are not reported. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics are provided. Statistical comparisons between arms were not performed for this primary endpoint.

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)				
ALT >2.5-5.0 X Baseline	3.6	2.6	9.1	
ALT >5.0 X Baseline	4.5	6.1	3.6	
AST >2.5-5.0 X Baseline	14.5	14	9.2	
AP >2.5-5.0 X Baseline	6.3	2.6	5.5	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with system organ class (SOC) AE incidence of >= 4 participants in one treatment group

End point title	Percentage of participants with system organ class (SOC) AE incidence of >= 4 participants in one treatment group

End point description:

A SOC is the highest level of terminology used to describe disorders of the human body, and distinguishes by either anatomical or physiological systems, disease origin or purpose. SOC AE incidence greater than or equal to 4 in one treatment group are presented. SOC AE incidence which did not achieve this threshold are not reported. SOC are based on MedDRA version 17.0. The population analyzed was all randomized participants who received at least one dose of IV study therapy, based on the therapy they actually received.

End point type	Primary

End point timeframe:

Up to 14 days following completion of all study therapy (up to Day 28)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	116	114	
Units: Percentage of participants				
number (not applicable)				
Blood and lymphatic system disorders	4.3	0.9	5.3	
Cardiac disorders	2.6	3.4	2.6	
Gastrointestinal disorders	18.8	17.2	13.2	
General disorders admin. site conditions	7.7	5.2	3.5	
Infections and infestations	11.1	7.8	7	
Injury, poisoning, procedural complications	4.3	6.9	5.3	
Investigations	11.1	10.3	12.3	
Nervous system disorders	1.7	3.4	4.4	
Psychiatric disorders	3.4	3.4	3.5	
Renal and urinary disorders	1.7	1.7	3.5	

Respiratory, thoracic, mediastinal disorders	1.7	4.3	6.1	
Skin, subcutaneous tissue disorders	4.3	1.7	1.8	
Vascular disorders	2.6	6	6.1	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Blood
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	5.1

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Blood
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	0.1

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff.-Card. dis.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	5

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. -Card. dis.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	6.3

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - GI Dis.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	15.3

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - GI Dis.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	13.6

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. -Gen.dis.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	11

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. -Gen.dis.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	7.8

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Infct.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	12

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Infct.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	8

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. -Inj.Pois.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	5.1

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. -Inj.Pois.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	8.5

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Inv.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	7.4

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Inv.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	6.5

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Nerv.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	2.2

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Nerv.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	4.7

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Psych.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	5.4

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Psych.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	5.5

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Renal

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Placebo + IPM/CIL v Relebactam 250 mg + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	3

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Renal
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	3

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff.- Resp.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	0.7

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff.- Resp.
Statistical analysis description:	
Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-1.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	4.4

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Skin

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	8.1

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Skin

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	4.5

Statistical analysis title	Relebactam 250 mg - Placebo: % Diff. - Vasc.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	2

Statistical analysis title	Relebactam 125 mg - Placebo: % Diff. - Vasc.

Statistical analysis description:

Difference in percentage based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	6.6

Secondary: Percentage of participants with a favorable clinical response at completion of IV study therapy in participants who have imipenem-resistant, gram-negative cIAI infections.

End point title	Percentage of participants with a favorable clinical response at completion of IV study therapy in participants who have imipenem-resistant, gram-negative cIAI infections.

End point description:

A favorable clinical response is assessed by the clinical investigator as a cure, and is defined as a situation where all or most pre-therapy signs and symptoms of the index infection have resolved, or returned to pre-infection status, and no additional antibiotic therapy is required. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; (4) received ≥ 96 hours of IV study therapy; and (5) had imipenem-resistant, gram negative cIAI infections.

End point type	Secondary

End point timeframe:

4 to 14 days post initiation of IV study therapy (up to postrandomization Day 14).

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14[9]	9[10]	11[11]	
Units: Percentage of participants				
number (confidence interval 95%)	100 (76.8 to 100)	100 (66.4 to 100)	100 (71.5 to 100)	

Notes:

[9] - Had imipenem-resistant, gram negative cIAI infections.

[10] - Had imipenem-resistant, gram negative cIAI infections.

[11] - Had imipenem-resistant, gram negative cIAI infections.

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference
Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	Fisher exact
Parameter estimate	Percentage Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	Fisher exact
Parameter estimate	Percentage Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Percentage of participants with a favorable clinical response at early follow-up

End point title	Percentage of participants with a favorable clinical response at

	early follow-up

End point description:

A favorable clinical response is assessed by the clinical investigator as a cure, and is defined as a situation where all or most pre-therapy signs and symptoms of the index infection have resolved, or returned to pre-infection status, and no additional antibiotic therapy is required. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy.

End point type	Secondary

End point timeframe:

Up to 9 days following completion of all study therapy (up to Day 23)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	86	81	
Units: Percentage of participants				
number (confidence interval 95%)	94.9 (87.5 to 98.6)	94.2 (87 to 98.1)	96.3 (89.6 to 99.2)	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	6

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.002
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	5.3

Secondary: Percentage of participants with a favorable microbiological response at completion of IV study therapy

End point title	Percentage of participants with a favorable microbiological response at completion of IV study therapy

End point description:

A favorable microbiological response is assessed by the clinical investigator, and is defined as the eradication or presumptive eradication of all bacterial pathogens identified at baseline. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy.

End point type	Secondary

End point timeframe:

Up to 14 days post-initiation of IV study therapy (up to postrandomization Day 14)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	86	84	
Units: Percentage of participants				
number (confidence interval 95%)	97.6 (91.6 to 99.7)	100 (95.8 to 100)	97.6 (91.7 to 99.7)	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Two participants with indeterminate or missing response were excluded from the analysis.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	6.2

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Two participants with indeterminate or missing response were excluded from the analysis.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	8.3

Secondary: Percentage of participants with a favorable microbiological response at early follow-up

End point title	Percentage of participants with a favorable microbiological response at early follow-up

End point description:

A favorable microbiological response is assessed by the clinical investigator, and is defined as the eradication or presumptive eradication of all bacterial pathogens identified at baseline. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy.

End point type	Secondary

End point timeframe:

Up to 9 days following completion of all study therapy (up to Day 23)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	82	80	
Units: Percentage of participants				
number (confidence interval 95%)	97.4 (91 to 99.7)	97.6 (91.5 to 99.7)	97.5 (91.3 to 99.7)	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Eight participants with indeterminate or missing response were excluded from the analysis.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	6.4

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Eight participants with indeterminate or missing response were excluded from the analysis.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	6.5

Secondary: Percentage of participants with a favorable clinical response at late follow-up

End point title	Percentage of participants with a favorable clinical response at late follow-up

End point description:

A favorable clinical response is assessed by the clinical investigator as a cure, and is defined as a situation where all or most pre-therapy signs and symptoms of the index infection have resolved, or returned to pre-infection status, and no additional antibiotic therapy is required. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy.

End point type	Secondary

End point timeframe:

Up to 42 days following completion of all study therapy (up to Day 56)

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	85	79	
Units: Percentage of participants				
number (confidence interval 95%)	93.7 (85.8 to 97.9)	95.3 (88.4 to 98.7)	94.9 (87.5 to 98.6)	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.002
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	6.9

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference
Statistical analysis description: Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification.	
Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	8.2

Secondary: Percentage of participants with a favorable microbiological response at late follow-up

End point title	Percentage of participants with a favorable microbiological response at late follow-up
End point description: A favorable microbiological response is assessed by the clinical investigator, and is defined as the eradication or presumptive eradication of all bacterial pathogens identified at baseline. The ME population was analyzed, defined as participants who: (1) met the protocol definition of cIAI; (2) had a pre-study/post operative culture from the site of infection grew at least one Gram-negative enteric and/or anaerobic pathogen; (3) had no significant deviations from the protocol that could impact the efficacy assessment; and (4) received ≥ 96 hours of IV study therapy.	
End point type	Secondary
End point timeframe: Up to 42 days following completion of all study therapy up to Day 56)	

End point values	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	81	78	
Units: Percentage of participants				
number (confidence interval 95%)	96.2 (89.2 to 99.2)	97.5 (91.4 to 99.7)	96.2 (89.2 to 99.2)	

Statistical analyses

Statistical analysis title	Relebactam 250 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Eight participants with indeterminate or missing response were excluded from the analysis.

Comparison groups	Relebactam 250 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	7.4

Statistical analysis title	Relebactam 125 mg - Placebo: Treatment Difference

Statistical analysis description:

Non-inferiority test based on unconditional asymptotic Miettinen and Nurminen method without stratification. Eight participants with indeterminate or missing response were excluded from the analysis.

Comparison groups	Relebactam 125 mg + IPM/CIL v Placebo + IPM/CIL
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Percentage Difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	8.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During study therapy and the protocol-specified follow-up period following end of study therapy (up to 28 days for non-serious AEs and up to 56 days for serious drug-related AEs)

Adverse event reporting additional description:

Population analyzed is all randomized participants who received at least one dose of IV study therapy. Participants with All-Cause Mortality were determined by the investigator to include some participants discontinued due to an adverse event, and progressive disease.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Relebactam 250 mg + IPM/CIL

Reporting group description:

Relebactam 250 mg and imipenem/cilastatin (IPM/CIL) 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Reporting group title	Relebactam 125 mg + IPM/CIL

Reporting group description:

Relebactam 125 mg and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Reporting group title	Placebo + IPM/CIL

Reporting group description:

Placebo for relebactam and IPM/CIL 500 mg were administered by IV separately, and concurrently over a 30-minute interval, every 6 hours for a minimum of 96 hours.

Serious adverse events	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 117 (3.42%)	11 / 116 (9.48%)	8 / 114 (7.02%)
number of deaths (all causes)	0	3	0
number of deaths resulting from adverse events	0	3	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign gastrointestinal neoplasm			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Mucinous adenocarcinoma of appendix			
subjects affected / exposed	0 / 117 (0.00%)	0 / 116 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Post procedural bile leak			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Procedural pain			
subjects affected / exposed	0 / 117 (0.00%)	0 / 116 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 117 (0.00%)	0 / 116 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound evisceration			
subjects affected / exposed	1 / 117 (0.85%)	0 / 116 (0.00%)	0 / 114 (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
Suture rupture			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 116 (0.00%)	0 / 114 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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 and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 116 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Ileus paralytic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 116 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal infarction			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 117 (0.00%)	0 / 116 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Pancreatitis acute			

subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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			
Cholelithiasis obstructive			
subjects affected / exposed	0 / 117 (0.00%)	0 / 116 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 117 (0.00%)	0 / 116 (0.00%)	1 / 114 (0.88%)
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 consolidation			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Pleural effusion			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Pulmonary embolism			
subjects affected / exposed	0 / 117 (0.00%)	0 / 116 (0.00%)	2 / 114 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Liver abscess			
subjects affected / exposed	1 / 117 (0.85%)	0 / 116 (0.00%)	0 / 114 (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
Postoperative wound infection			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (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
Septic shock			
subjects affected / exposed	0 / 117 (0.00%)	1 / 116 (0.86%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1

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

Non-serious adverse events	Relebactam 250 mg + IPM/CIL	Relebactam 125 mg + IPM/CIL	Placebo + IPM/CIL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 117 (13.68%)	15 / 116 (12.93%)	13 / 114 (11.40%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 117 (5.98%)	6 / 116 (5.17%)	5 / 114 (4.39%)
occurrences (all)	8	6	5
Nausea			
subjects affected / exposed	8 / 117 (6.84%)	9 / 116 (7.76%)	8 / 114 (7.02%)
occurrences (all)	9	9	9
Vomiting			

subjects affected / exposed occurrences (all)	7 / 117 (5.98%) 7	9 / 116 (7.76%) 9	3 / 114 (2.63%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported