Clinical trial results:
A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Piperacillin/Tazobactam in Subjects with Hospital-Acquired Bacterial Pneumonia or Ventilator-Associated Bacterial Pneumonia

Summary

EudraCT number	2015-000246-34
Trial protocol	DE EE LV BG PT LT FR ES HR CZ IT
Global end of trial date	03 April 2019

Results information

Result version number	v1 (current)
This version publication date	19 April 2020
First version publication date	19 April 2020

Trial information

Trial identification

Sponsor protocol code	7655A-014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02493764
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC-CTI: 163240

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	03 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to compare treatment with a fixed-dose combination (FDC) of imipenem/relebactam/cilastatin (IMI/REL) with a FDC of piperacillin/tazobactam (PIP/TAZ) in participants with hospital-acquired or ventilator-associated bacterial pneumonia (HABP or VAPB, respectively). The primary hypothesis is that IMI/REL is non-inferior to PIP/TAZ in the percentage of participants with a favorable clinical response.

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	24 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Brazil: 44
Country: Number of subjects enrolled	Bulgaria: 21
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Colombia: 21
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Estonia: 12
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Georgia: 18
Country: Number of subjects enrolled	Guatemala: 5
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 43
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Mexico: 34
Country: Number of subjects enrolled	Norway: 6

Country: Number of subjects enrolled	Philippines: 27
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Romania: 30
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Serbia: 7
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Turkey: 13
Country: Number of subjects enrolled	Ukraine: 128
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	537
EEA total number of subjects	128

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)	306
From 65 to 84 years	198
85 years and over	33

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult male and female participants requiring intravenous (IV) therapy for hospital-acquired bacterial pneumonia (HABP) or ventilator-assisted bacterial pneumonia (VABP) were screened for inclusion.

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	IMI/REL

Arm description:

Participants received imipenem 500 mg + relebactam 250 mg + cilastatin 500 mg as a FDC administered IV every 6 hours for a minimum of 7 days, up to 14 days. At the start of IMI/REL treatment, participants were treated empirically with 600 mg open-label linezolid administered IV every 12 hours until methicillin-resistant Staphylococcus aureus (MRSA) was ruled out. Participants with confirmed MRSA infection continued to receive 600 mg linezolid every 12 hours for a minimum of 7 days, up to 14 days total.

Arm type	Experimental
Investigational medicinal product name	Imipenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Imipenem 500 mg as part of a FDC administered by IV every 6 hours for a minimum of 7 days, up to 14 days.

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

Dosage and administration details:

Relebactam 250 mg as part of a FDC administered by IV every 6 hours for a minimum of 7 days, up to 14 days.

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

Dosage and administration details:

Cilastatin 500 mg as part of a FDC administered by IV every 6 hours for a minimum of 7 days, up to 14 days.

Investigational medicinal product name	Linezolid
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Linezolid 600 mg administered open-label by IV every 12 hours for up to 14 days.

Arm title	PIP/TAZ

Arm description:

Participants received piperacillin 4000 mg + tazobactam 500 mg as a FDC administered IV every 6 hours for a minimum of 7 days, up to 14 days. At the start of PIP/TAZ treatment, participants were treated empirically with 600 mg open-label linezolid administered IV every 12 hours until MRSA was ruled out. Participants with confirmed MRSA infection continued to receive 600 mg linezolid every 12 hours for a minimum of 7 days, up to 14 days total.

Arm type	Active comparator
Investigational medicinal product name	Piperacillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Piperacillin 4000 mg as part of a FDC administered by IV every 6 hours for a minimum of 7 days, up to 14 days.

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

Dosage and administration details:

Tazobactam 500 mg as part of a FDC administered by IV every 6 hours for a minimum of 7 days, up to 14 days.

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

Dosage and administration details:

Linezolid 600 mg administered open-label by IV every 12 hours for up to 14 days.

Number of subjects in period 1	IMI/REL	PIP/TAZ
Started	268	269
Completed	185	187
Not completed	83	82
Participant moved	17	5
Withdrawal parent/guardian	-	1
Physician decision	1	1
Consent withdrawn by subject	11	7
Death	44	58
Adverse event	2	2

Lost to follow-up	2	1
Protocol deviation	6	7

Baseline characteristics

Reporting groups	
Reporting group title	IMI/REL
Reporting group description:	
Participants received imipenem 500 mg + relebactam 250 mg + cilastatin 500 mg as a FDC administered IV every 6 hours for a minimum of 7 days, up to 14 days. At the start of IMI/REL treatment, participants were treated empirically with 600 mg open-label linezolid administered IV every 12 hours until methicillin-resistant Staphylococcus aureus (MRSA) was ruled out. Participants with confirmed MRSA infection continued to receive 600 mg linezolid every 12 hours for a minimum of 7 days, up to 14 days total.	
Reporting group title	PIP/TAZ
Reporting group description:	
Participants received piperacillin 4000 mg + tazobactam 500 mg as a FDC administered IV every 6 hours for a minimum of 7 days, up to 14 days. At the start of PIP/TAZ treatment, participants were treated empirically with 600 mg open-label linezolid administered IV every 12 hours until MRSA was ruled out. Participants with confirmed MRSA infection continued to receive 600 mg linezolid every 12 hours for a minimum of 7 days, up to 14 days total.	

Reporting group values	IMI/REL	PIP/TAZ	Total
Number of subjects	268	269	537
Age categorical Units: Subjects			
Adults (18-64 years)	154	152	306
From 65-84 years	98	100	198
85 years and over	16	17	33
Age Continuous Units: Years			
arithmetic mean	60.4	58.9	
standard deviation	± 17.0	± 18.4	-
Sex: Female, Male Units: Participants			
Female	86	78	164
Male	182	191	373
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	8	13
Asian	42	37	79
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	4	6	10
White	208	209	417
More than one race	9	7	16
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	56	55	111
Not Hispanic or Latino	209	205	414
Unknown or Not Reported	3	9	12

End points

End points reporting groups

Reporting group title	IMI/REL

Reporting group description:

Participants received imipenem 500 mg + relebactam 250 mg + cilastatin 500 mg as a FDC administered IV every 6 hours for a minimum of 7 days, up to 14 days. At the start of IMI/REL treatment, participants were treated empirically with 600 mg open-label linezolid administered IV every 12 hours until methicillin-resistant Staphylococcus aureus (MRSA) was ruled out. Participants with confirmed MRSA infection continued to receive 600 mg linezolid every 12 hours for a minimum of 7 days, up to 14 days total.

Reporting group title	PIP/TAZ

Reporting group description:

Participants received piperacillin 4000 mg + tazobactam 500 mg as a FDC administered IV every 6 hours for a minimum of 7 days, up to 14 days. At the start of PIP/TAZ treatment, participants were treated empirically with 600 mg open-label linezolid administered IV every 12 hours until MRSA was ruled out. Participants with confirmed MRSA infection continued to receive 600 mg linezolid every 12 hours for a minimum of 7 days, up to 14 days total.

Primary: Percentage of participants in the modified intention-to-treat (MITT) population with a favorable clinical response (FCR) at early follow-up (EFU) visit

End point title	Percentage of participants in the modified intention-to-treat (MITT) population with a favorable clinical response (FCR) at early follow-up (EFU) visit

End point description:

The percentage of participants with a FCR at EFU was determined for each arm. Favorable clinical response at EFU was defined as either "sustained cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] with no evidence of resurgence and no additional antibiotics are required) or "cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] and no additional antibiotics are required). The MITT population includes all randomized participants who received ≥1 dose of study treatment and did not have only gram-positive cocci on Gram stain of the baseline lower respiratory tract (LRT) specimen.

End point type	Primary

End point timeframe:

Up to 16 days after end of therapy (up to 30 days)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	267		
Units: Percentage of participants				
number (not applicable)	61.0	55.8		

Statistical analyses

Statistical analysis title	Adjusted difference in FCR

Statistical analysis description:

Non-inferiority was declared when the lower bound of the 2-sided 95% CI for the difference in FCR

(IMI/REL minus PIP/TAZ) was > 12.5 percentage points.

Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	t-test, 1-sided
Parameter estimate	Adjusted difference in FCR
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	13.2

Secondary: Percentage of participants with all-cause mortality (ACM) through Day 28 in the MITT population

End point title	Percentage of participants with all-cause mortality (ACM) through Day 28 in the MITT population

End point description:

The percentage of participants in the MITT population with mortality due to any cause from randomization through Day 28 was determined for each arm. The MITT population includes all randomized participants who received ≥1 dose of study treatment and did not have only gram-positive cocci on Gram stain of the baseline LRT specimen.

End point type	Secondary

End point timeframe:

Up to 28 days

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	267		
Units: Percentage of participants				
number (not applicable)	15.9	21.3		

Statistical analyses

Statistical analysis title	Adjusted difference in all-cause mortality

Statistical analysis description:

Non-inferiority was declared when the upper bound of the 2-sided 95% confidence interval (CI) for the difference in mortality (IMI/REL minus PIP/TAZ) was < 10 percentage points.

Comparison groups	IMI/REL v PIP/TAZ

Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	t-test, 1-sided
Parameter estimate	Adjusted difference in ACM
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	1.2

Secondary: Percentage of participants with ≥1 adverse event (AE)

End point title	Percentage of participants with ≥1 adverse event (AE)

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All participants who received ≥1 dose of study therapy are included.

End point type	Secondary

End point timeframe:

Up to 30 days

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	269		
Units: Percentage of participants				
number (not applicable)	85.0	86.6		

Statistical analyses

Statistical analysis title	Difference in % with AE vs PIP/TAZ
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % with AE
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	4.3

Secondary: Percentage of participants discontinuing study therapy due to an AE

End point title	Percentage of participants discontinuing study therapy due to an AE

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All participants who received ≥1 dose of study therapy are included.

End point type	Secondary

End point timeframe:

Up to 14 days

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	269		
Units: Percentage of participants				
number (not applicable)	5.6	8.2		

Statistical analyses

Statistical analysis title	Difference in % discontinuing vs PIP/TAZ
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % discontinuing
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	1.8

Secondary: Percentage of participants with ACM in the microbiological modified intention-to-treat (mMITT) population

End point title	Percentage of participants with ACM in the microbiological modified intention-to-treat (mMITT) population

End point description:

The percentage of participants in the mMITT population with mortality due to any cause from randomization through Day 28 was determined for each arm. The mMITT population includes all randomized participants who received ≥1 dose of study treatment and did not have only gram-positive cocci only on baseline Gram stain and who have a baseline bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity.

End point type	Secondary
End point timeframe:	
Up to 28 days	

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	218		
Units: Percentage of participants				
number (not applicable)	16.7	20.2		

Statistical analyses

Statistical analysis title	Adjusted difference in all-cause mortality
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in ACM
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	3.6

Secondary: Percentage of participants with ACM at EFU in the MITT population

End point title	Percentage of participants with ACM at EFU in the MITT population
End point description:	
The percentage of participants in the MITT population with mortality due to any cause from randomization through EFU was determined for each arm. The MITT population includes all randomized participants who received ≥1 dose of study treatment and did not have only gram-positive cocci on Gram stain of the baseline specimen.	
End point type	Secondary
End point timeframe:	
Up to 16 days after end of therapy (up to 30 days)	

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	267		
Units: Percentage of participants				
number (not applicable)	14.8	19.5		

Statistical analyses

Statistical analysis title	Adjusted difference in all-cause mortality

Statistical analysis description:

Non-inferiority was declared when the upper bound of the 2-sided 95% CI for the difference in mortality (IMI/REL minus PIP/TAZ) was ≥ 10 percentage points.

Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in ACM
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	1.7

Secondary: Percentage of participants with ACM at EFU in the mMITT population

End point title	Percentage of participants with ACM at EFU in the mMITT population

End point description:

The percentage of participants in the mMITT population with mortality due to any cause from randomization through EFU was determined for each arm. The mMITT population includes all randomized participants who received ≥1 dose of study treatment and did not have only gram-positive cocci only on baseline Gram stain and who have a baseline bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity.

End point type	Secondary

End point timeframe:

Up to 16 days after end of therapy (up to 30 days)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	218		
Units: Percentage of participants				
number (not applicable)	15.3	18.3		

Statistical analyses

Statistical analysis title	Adjusted difference in all-cause mortality
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in ACM
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	3.8

Secondary: Percentage of participants in the clinically evaluable (CE) population with a FCR at on-therapy visit 1 (OTX1) [Day 3]

End point title	Percentage of participants in the clinically evaluable (CE) population with a FCR at on-therapy visit 1 (OTX1) [Day 3]

End point description:

The percentage of participants with a FCR at OTX1 was determined for each arm. Favorable clinical response at OTX1 was defined as "improved" (majority of pre-therapy signs and symptoms of the index infection have improved or resolved [or returned to "pre-infection status"]). The CE population is all randomized participants with ≥1 dose of study therapy; had not only gram-positive cocci on baseline Gram stain; met important entry criteria; had no protocol deviations; received minimum duration of IV therapy; and have Day 3 clinical response data.

End point type	Secondary

End point timeframe:

Day 3 (OTX1)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	162		
Units: Percentage of participants				
number (not applicable)	70.8	72.8		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	7.8

Secondary: Percentage of participants in the CE population with a FCR at OTX2 (Day 6)

End point title	Percentage of participants in the CE population with a FCR at OTX2 (Day 6)

End point description:

The percentage of participants with a FCR at OTX2 was determined for each arm. Favorable clinical response at OTX2 was defined as "improved" (majority of pre-therapy signs and symptoms of the index infection have improved or resolved [or returned to "pre-infection status"]). The CE population is all randomized participants with ≥1 dose of study therapy; had not only gram-positive cocci on baseline Gram stain; met important entry criteria; had no protocol deviations; received minimum duration of IV therapy; and have Day 6 clinical response data.

End point type	Secondary

End point timeframe:

Day 6 (OTX2)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	156		
Units: Percentage of participants				
number (not applicable)	85.5	87.8		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	-2.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	5.5

Secondary: Percentage of participants in the CE population with a FCR at OTX3 (Day 10)

End point title	Percentage of participants in the CE population with a FCR at OTX3 (Day 10)

End point description:

The percentage of participants with a FCR at OTX3 was determined for each arm. Favorable clinical response at OTX3 was defined as "improved" (majority of pre-therapy signs and symptoms of the index infection have improved or resolved [or returned to "pre-infection status"]). The CE population is all randomized participants with ≥1 dose of study therapy; had not only gram-positive cocci on baseline Gram stain; met important entry criteria; had no protocol deviations; received minimum duration of IV therapy; and have Day 10 clinical response data.

End point type	Secondary

End point timeframe:

Day 10 (OTX3)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	73		
Units: Percentage of participants				
number (not applicable)	89.6	83.6		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	18.4

Secondary: Percentage of participants in the CE population with a FCR at EOT visit

End point title	Percentage of participants in the CE population with a FCR at EOT visit

End point description:

The percentage of participants with a FCR at EOT was determined for each arm. Favorable clinical response at EOT was defined as either "cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] and no additional antibiotics are required) or "improved" (the majority of pre-therapy signs and symptoms of the index infection have improved or resolved [or returned to "pre-infection status"] and no additional antibiotics are required). The CE population is all randomized participants with ≥1 dose of study therapy; had not only gram-positive cocci on baseline Gram stain; met important entry criteria; had no protocol deviations; received minimum duration of IV therapy; and have EOT clinical response data.

End point type	Secondary

End point timeframe:

From Day 7 to Day 14

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	163		
Units: Percentage of participants				
number (not applicable)	84.7	85.3		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	7.4

Secondary: Percentage of participants in the CE population with a FCR at Day 28

End point title	Percentage of participants in the CE population with a FCR at Day 28

End point description:

The percentage of participants with a FCR at Day 28 was determined for each arm. Favorable clinical response at Day 28 was defined as either "sustained cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] with no evidence of resurgence and no additional antibiotics are required) or "cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] and no additional antibiotics are required). The CE population is all randomized participants with ≥1 dose of study therapy; had not only gram-positive cocci on baseline Gram stain; met important entry criteria; had no protocol deviations; received minimum duration of IV therapy; and have Day 28 clinical response data.

End point type	Secondary

End point timeframe:

Day 28

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	119		
Units: Percentage of participants				
number (not applicable)	70.5	75.6		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.3
upper limit	7.5

Secondary: Percentage of participants in the CE population with a FCR at EFU visit

End point title	Percentage of participants in the CE population with a FCR at EFU visit

End point description:

The percentage of participants with a FCR at EFU was determined for each arm. Favorable clinical response at EFU was defined as either "sustained cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] with no evidence of resurgence and no additional antibiotics are required) or "cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] and no additional antibiotics are required). The CE population is all randomized participants with ≥1 dose of study therapy; had not only gram-positive cocci on baseline Gram stain; met important entry criteria; had no protocol deviations; received minimum duration of IV therapy; and have EFU clinical response data.

End point type	Secondary

End point timeframe:

Up to 16 days after end of therapy (up to Day 30)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	144		
Units: Percentage of participants				
number (not applicable)	74.3	79.4		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.6
upper limit	6.4

Secondary: Percentage of participants in the MITT population with a FCR at OTX1 (Day 3)

End point title	Percentage of participants in the MITT population with a FCR at OTX1 (Day 3)

End point description:

The percentage of participants with a FCR at OTX1 was determined for each arm. Favorable clinical response at OTX1 was defined as "improved" (majority of pre-therapy signs and symptoms of the index infection have improved or resolved [or returned to "pre-infection status"]). The MITT population includes all randomized participants who received ≥1 dose of study treatment, did not have only gram-positive cocci on Gram stain of the baseline specimen, and have Day 3 data.

End point type	Secondary

End point timeframe:

Day 3 (OTX1)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	252		
Units: Percentage of participants				
number (not applicable)	68.0	64.7		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	11.6

Secondary: Percentage of participants in the MITT population with a FCR at OTX2 (Day 6)

End point title	Percentage of participants in the MITT population with a FCR at OTX2 (Day 6)

End point description:

The percentage of participants with a FCR at OTX2 was determined for each arm. Favorable clinical response at OTX2 was defined as "improved" (majority of pre-therapy signs and symptoms of the index infection have improved or resolved [or returned to "pre-infection status"]). The MITT population includes all randomized participants who received ≥1 dose of study treatment, did not have only gram-positive cocci on Gram stain of the baseline specimen, and have Day 6 data.

End point type	Secondary

End point timeframe:

Day 6 (OTX2)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	225		
Units: Percentage of participants				
number (not applicable)	83.5	83.1		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	7.4

Secondary: Percentage of participants in the MITT population with a FCR at OTX3 (Day 10)

End point title	Percentage of participants in the MITT population with a FCR at OTX3 (Day 10)

End point description:

The percentage of participants with a FCR at OTX3 was determined for each arm. Favorable clinical response at OTX3 was defined as "improved" (majority of pre-therapy signs and symptoms of the index infection have improved or resolved [or returned to "pre-infection status"]). The MITT population includes all randomized participants who received ≥1 dose of study treatment, did not have only gram-positive cocci on Gram stain of the baseline specimen, and have Day 10 data.

End point type	Secondary

End point timeframe:

Day 10 (OTX3)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	102		
Units: Percentage of participants				
number (not applicable)	83.5	80.4		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	14.2

Secondary: Percentage of participants in the MITT population with a FCR at EOT

End point title	Percentage of participants in the MITT population with a FCR at EOT

End point description:

The percentage of participants with a FCR at EOT was determined for each arm. Favorable clinical response at EOT was defined as either "cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] and no additional antibiotics are required) or "improved" (the majority of pre-therapy signs and symptoms of the index infection have improved or resolved [or returned to "pre-infection status"] and no additional antibiotics are required). The MITT population includes all randomized participants who received ≥1 dose of study treatment, did not have only gram-positive cocci on Gram stain of the baseline specimen, and have EOT data.

End point type	Secondary

End point timeframe:

From Day 7 to Day 14

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	267		
Units: Percentage of participants				
number (not applicable)	74.2	69.7		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	12

Secondary: Percentage of participants in the MITT population with a FCR at Day 28

End point title	Percentage of participants in the MITT population with a FCR at Day 28

End point description:

The percentage of participants with a FCR at Day 28 was determined for each arm. Favorable clinical response at Day 28 was defined as either "sustained cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] with no evidence of resurgence and no additional antibiotics are required) or "cure" (all pre-therapy signs and symptoms of the index infection have resolved [or returned to "pre-infection status"] and no additional antibiotics are required). The MITT population includes all randomized participants who received ≥1 dose of study treatment, did not have only gram-positive cocci on Gram stain of the baseline specimen, and have Day 28 data.

End point type	Secondary

End point timeframe:

Day 28

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	267		
Units: Percentage of participants				
number (not applicable)	51.9	50.6		

Statistical analyses

Statistical analysis title	Adjusted difference in favorable clinical response
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	531
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FCR
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	9.4

Secondary: Percentage of participants in the mMITT population with a favorable microbiological response (FMR) at end of treatment (EOT) visit

End point title	Percentage of participants in the mMITT population with a favorable microbiological response (FMR) at end of treatment (EOT) visit

End point description:

The percentage of participants with a FMR at EOT was determined for each arm. Favorable microbiological response at EOT was defined as either "eradication" (a lower respiratory tract culture taken at EOT showing eradication of baseline pathogen) or "presumed eradication" (no specimen collected because the participant deemed clinically cured or improved). The mMITT population includes all randomized participants who received ≥1 dose of study treatment, did not have only gram-positive cocci only on baseline Gram stain, have a baseline bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity, and have EOT data.

End point type	Secondary

End point timeframe:

From Day 7 to Day 14

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	218		
Units: Percentage of participants				
number (not applicable)	77.2	67.9		

Statistical analyses

Statistical analysis title	Adjusted difference in FMR
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FMR
Point estimate	9.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	17.9

Secondary: Percentage of participants in the mMITT population with a FMR at EFU visit

End point title	Percentage of participants in the mMITT population with a FMR at EFU visit

End point description:

The percentage of participants with a FMR at EFU was determined for each arm. Favorable microbiological response at EOT was defined as either "eradication" (a lower respiratory tract culture taken at EFU showing eradication of baseline pathogen) or "presumed eradication" (no specimen collected because the participant deemed clinically cured or improved). The mMITT population includes all randomized participants who received ≥1 dose of study treatment, did not have only gram-positive cocci only on baseline Gram stain, have a baseline bacterial pathogen identified as the cause of HABP/VABP against which IMI/REL has been shown to have antibacterial activity, and have EFU data.

End point type	Secondary

End point timeframe:

Up to 16 days after end of therapy (up to Day 30)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	218		
Units: Percentage of participants				
number (not applicable)	67.9	61.9		

Statistical analyses

Statistical analysis title	Adjusted difference in FMR
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FMR
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	15

Secondary: Percentage of participants in the microbiologically evaluable (ME) population with a FMR at EOT visit

End point title	Percentage of participants in the microbiologically evaluable (ME) population with a FMR at EOT visit

End point description:

The percentage of participants with a FMR at EOT was determined for each arm. Favorable microbiological response at EOT was defined as either "eradication" (a lower respiratory tract culture taken at EOT showing eradication of baseline pathogen) or "presumed eradication" (no specimen collected because the participant deemed clinically cured or improved). The ME population is all randomized participants with ≥1 dose of study therapy; not only gram-positive cocci on baseline Gram stain; IMI/REL-sensitive baseline pathogen as cause of HABP/VABP; met entry criteria; no protocol deviations; received minimum duration of IV therapy; have microbiological EOT data and LRT culture available.

End point type	Secondary

End point timeframe:

From Day 7 to Day 14

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	133		
Units: Percentage of participants				
number (not applicable)	87.1	85.5		

Statistical analyses

Statistical analysis title	Adjusted difference in FMR
Comparison groups	IMI/REL v PIP/TAZ

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FMR
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	11

Secondary: Percentage of participants in the ME population with a FMR at EFU visit

End point title	Percentage of participants in the ME population with a FMR at EFU visit

End point description:

The percentage of participants with a FMR at EOT was determined for each arm. Favorable microbiological response at EOT was defined as either "eradication" (a lower respiratory tract culture taken at EOT showing eradication of baseline pathogen) or "presumed eradication" (no specimen collected because the participant deemed clinically cured or improved). The ME population is all randomized participants with ≥1 dose of study therapy; not only gram-positive cocci on baseline Gram stain; IMI/REL-sensitive baseline pathogen as cause of HABP/VABP; met entry criteria; no protocol deviations; received minimum duration of IV therapy; have microbiological EFU data and LRT culture available.

End point type	Secondary

End point timeframe:

Up to 16 days after end of therapy (up to Day 30)

End point values	IMI/REL	PIP/TAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	117		
Units: Percentage of participants				
number (not applicable)	89.9	86.4		

Statistical analyses

Statistical analysis title	Adjusted difference in FMR
Comparison groups	IMI/REL v PIP/TAZ
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in FMR
Point estimate	4.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	14.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days

Adverse event reporting additional description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All randomized participants who received ≥1 dose of intravenous (IV) study therapy are included in the analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	PIP/TAZ

Reporting group description:

Participants received piperacillin 4000 mg + tazobactam 500 mg as a FDC administered IV every 6 hours for a minimum of 7 days, up to 14 days. At the start of PIP/TAZ treatment, participants were treated empirically with 600 mg open-label linezolid administered IV every 12 hours until MRSA was ruled out. Participants with confirmed MRSA infection continued to receive 600 mg linezolid every 12 hours for a minimum of 7 days, up to 14 days total.

Reporting group title	IMI/REL

Reporting group description:

Participants received imipenem 500 mg + relebactam 250 mg + cilastatin 500 mg as a FDC administered IV every 6 hours for a minimum of 7 days, up to 14 days. At the start of PIP/TAZ treatment, participants were treated empirically with 600 mg open-label linezolid administered IV every 12 hours until MRSA was ruled out. Participants with confirmed MRSA infection continued to receive 600 mg linezolid every 12 hours for a minimum of 7 days, up to 14 days total.

Serious adverse events	PIP/TAZ	IMI/REL	
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 269 (31.97%)	71 / 266 (26.69%)	
number of deaths (all causes)	58	44	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	2 / 269 (0.74%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	2 / 269 (0.74%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Haematoma			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemodynamic instability			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Brain death			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death			
subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	6 / 269 (2.23%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 6	0 / 1	
Vascular stent thrombosis			

subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 269 (0.37%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Aspiration			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 269 (0.00%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural fibrosis			

subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 269 (0.00%)	4 / 266 (1.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	2 / 269 (0.74%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 269 (0.00%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 269 (0.74%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory depression			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 269 (1.12%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 269 (0.37%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 269 (0.37%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Endotracheal intubation complication			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant tissue necrosis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal shock			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Splenic rupture			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 269 (0.74%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrioventricular block complete			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bradycardia			

subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	7 / 269 (2.60%)	10 / 266 (3.76%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 6	0 / 9	
Cardiac failure			
subjects affected / exposed	2 / 269 (0.74%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 269 (0.74%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	2 / 269 (0.74%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiovascular insufficiency			
subjects affected / exposed	4 / 269 (1.49%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Myocardial infarction			

subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Basilar artery thrombosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain dislocation syndrome			
subjects affected / exposed	3 / 269 (1.12%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Brain oedema			
subjects affected / exposed	3 / 269 (1.12%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coma			

subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	3 / 269 (1.12%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lethargy			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Splenic lesion			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			

subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal ulcer			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	2 / 269 (0.74%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	8 / 269 (2.97%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure			
subjects affected / exposed	1 / 269 (0.37%)	2 / 266 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			

subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological infection			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 269 (1.12%)	6 / 266 (2.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 4	
Pneumonia acinetobacter			

subjects affected / exposed	1 / 269 (0.37%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 269 (1.12%)	3 / 266 (1.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 2	
Septic shock			
subjects affected / exposed	4 / 269 (1.49%)	7 / 266 (2.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 6	
Skin infection			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tuberculosis			

subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 269 (0.00%)	1 / 266 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 269 (0.37%)	0 / 266 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	PIP/TAZ	IMI/REL	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 269 (39.03%)	98 / 266 (36.84%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	18 / 269 (6.69%)	23 / 266 (8.65%)	
occurrences (all)	18	25	
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 269 (7.06%)	29 / 266 (10.90%)	
occurrences (all)	19	31	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	27 / 269 (10.04%)	28 / 266 (10.53%)	
occurrences (all)	28	30	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	20 / 269 (7.43%)	11 / 266 (4.14%)	
occurrences (all)	29	19	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	29 / 269 (10.78%)	21 / 266 (7.89%)	
occurrences (all)	32	22	
Respiratory, thoracic and mediastinal disorders			
Hydrothorax			
subjects affected / exposed	14 / 269 (5.20%)	11 / 266 (4.14%)	
occurrences (all)	17	11	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	24 / 269 (8.92%)	18 / 266 (6.77%)	
occurrences (all)	25	19	
Hyponatraemia			
subjects affected / exposed	3 / 269 (1.12%)	14 / 266 (5.26%)	
occurrences (all)	3	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2015	AM01: The primary purpose of the amendment was to modify inclusion/exclusion criteria.
22 April 2016	AM02: The primary purposes of the amendment were to modify inclusion/exclusion criteria.
23 August 2018	AM04: The primary purpose of the amendment was to modify microbiological response criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported