Clinical trial results:
A Multi-national Phase 3, 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	2018-003202-82
Trial protocol	FR RO
Global end of trial date	12 July 2022

Results information

Result version number	v1 (current)
This version publication date	24 June 2023
First version publication date	24 June 2023

Trial information

Trial identification

Sponsor protocol code	7655a-016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03583333
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, 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	12 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2022
Global end of trial reached?	Yes
Global end of trial date	12 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the efficacy and safety of a FDC of imipenem/cilastatin (IMI) and relebactam (REL) [IMI/REL, MK-7655A] compared to piperacillin/tazobactam (PIP/TAZ) in the treatment of adults diagnosed with Hospital-Acquired Bacterial Pneumonia (HABP) or Ventilator-Associated Bacterial Pneumonia (VABP). The primary hypothesis was that IMI/REL is non-inferior to PIP/TAZ as measured by the incidence rate of all-cause mortality through Day 28 post-randomization.

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	18 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	China: 204
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Philippines: 8
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Ukraine: 23
Worldwide total number of subjects	274
EEA total number of subjects	15

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)	170
From 65 to 84 years	100
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 54 centers in 8 countries.

Pre-assignment

Screening details:

Participants were randomized 1:1 to receive either FDC of imipenem/cilastatin (IMI) and relebactam (REL) [IMI/REL, MK-7655A], or piperacillin/tazobactam (PIP/TAZ).

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	IMI/REL FDC

Arm description:

Imipenem/cilastatin/relebactam (IMI/REL) was administered intravenously (IV) as a fixed-dose combination (FDC) at a dosage of 500 mg IMI/250 mg REL, once every 6 hours for a minimum 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	Linezolid
Investigational medicinal product code	
Other name	IMI/REL FDC, PIP/TAZ FDC
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use, Intravenous use

Dosage and administration details:

Open-label 600 mg Linezolid

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

Dosage and administration details:

500 mg Imipenem, 500 mg Cilastatin and 250 mg Relebactam powder FDC provided in a single vial

Arm title	PIP/TAZ FDC

Arm description:

Piperacillin/tazobactam (PIP/TAZ) was administered IV as a FDC at a dosage of 4000 mg PIP/500 mg TAZ once every 6 hours for a minimum 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 methicillin-resistant Staphylococcus aureus (MRSA) is 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	PIP/TAZ FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

4000 mg Piperacillin and 500 mg Tazobactam powder FDC provided in a single vial

Number of subjects in period 1	IMI/REL FDC	PIP/TAZ FDC
Started	138	136
Treated	134	136
Completed	90	106
Not completed	48	30
Consent withdrawn by subject	9	5
Physician decision	3	2
Death	12	7
Withdrawal by Parent/Guardian	16	10
Subject had Day 28 Visit Prior to Required Time	8	6

Baseline characteristics

Reporting groups	
Reporting group title	IMI/REL FDC
Reporting group description:	
Imipenem/cilastatin/relebactam (IMI/REL) was administered intravenously (IV) as a fixed-dose combination (FDC) at a dosage of 500 mg IMI/250 mg REL, once every 6 hours for a minimum 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 FDC
Reporting group description:	
Piperacillin/tazobactam (PIP/TAZ) was administered IV as a FDC at a dosage of 4000 mg PIP/500 mg TAZ once every 6 hours for a minimum 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 methicillin-resistant Staphylococcus aureus (MRSA) is 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 FDC	PIP/TAZ FDC	Total
Number of subjects	138	136	274
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	92	78	170
From 65-84 years	45	55	100
85 years and over	1	3	4
Age Continuous Units: Years			
arithmetic mean	55.9	59.2	
standard deviation	± 15.1	± 14.7	-
Sex: Female, Male Units: Participants			
Female	37	36	73
Male	101	100	201
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	110	102	212
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	27	33	60
More than one race	0	1	1
Unknown or Not Reported	0	0	0

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	8	12
Not Hispanic or Latino	134	128	262
Unknown or Not Reported	0	0	0
Randomization strata: Pneumonia type at baseline			
Participants were stratified by the following two pneumonia types at baseline: Non-ventilated hospital acquired bacterial pneumonia (HABP) and ventilated HABP/ventilator associated bacterial pneumonia (VABP).			
Units: Subjects			
Non-ventilated HABP	74	80	154
Ventilated HABP/VABP	64	56	120
Randomization strata: Acute Physiology and Chronic Health Evaluation (APACHE) II score at baseline			
APACHE score is a severity-of-disease classification system that is calculated from a participants age and 12 routine physiological measurements. Total scores are computed based on several measurements and range from 0 to 71 with higher scores corresponding to more severe disease and a higher risk of death. Participants were stratified by APACHE II score at baseline <15 vs. >15			
Units: Subjects			
APACHE II Score <15	65	61	126
APACHE II Score ≥15	73	75	148

End points

End points reporting groups

Reporting group title	IMI/REL FDC

Reporting group description:

Imipenem/cilastatin/relebactam (IMI/REL) was administered intravenously (IV) as a fixed-dose combination (FDC) at a dosage of 500 mg IMI/250 mg REL, once every 6 hours for a minimum 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 FDC

Reporting group description:

Piperacillin/tazobactam (PIP/TAZ) was administered IV as a FDC at a dosage of 4000 mg PIP/500 mg TAZ once every 6 hours for a minimum 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 methicillin-resistant Staphylococcus aureus (MRSA) is 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 with all-cause mortality through Day 28 in the modified intent to treat (MITT) population

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

End point description:

For each participant, survival status was assessed at Day 28 post-randomization and recorded on the electronic Case Report Form. The percentage of participants with all-cause mortality through Day 28 in the MITT population is presented. The MITT population consisting of all randomized participants who received at least 1 dose of IV study therapy and did not have the presence of positive cocci only on baseline Gram stain were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 28 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	136		
Units: Percentage of Participants				
number (not applicable)	11.2	5.9		

Statistical analyses

Statistical analysis title	Superiority Test
Comparison groups	IMI/REL FDC v PIP/TAZ FDC

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.938
Method	Miettinen & Nurminen
Parameter estimate	Adjusted difference in percentage
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	12.4

Statistical analysis title	Non-Inferiority Test
Comparison groups	IMI/REL FDC v PIP/TAZ FDC
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.024
Method	Miettinen & Nurminen method
Parameter estimate	Adjusted difference in percentage
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	12.4

Secondary: Percentage of participants achieving a favorable clinical response at early follow-up (EFU) visit in the MITT population

End point title	Percentage of participants achieving a favorable clinical response at early follow-up (EFU) visit in the MITT population

End point description:

Clinical response was defined as "Sustained cure" (All pretherapy signs and symptoms of the index infection have resolved or returned to preinfection status with no evidence of resurgence AND no additional antibiotic therapy was required for the index infection) or "Cure" (All pretherapy signs and symptoms of the index infection have resolved or returned to preinfection status AND no additional antibiotic therapy was required for the index infection). The percentage of participants achieving a favorable clinical response at EFU visit in the MITT population is presented. The MITT population consisting of all randomized participants who received at least 1 dose of IV study therapy and did not have the presence of positive cocci only on baseline Gram stain were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 27 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	136		
Units: Percentage of Participants				
number (not applicable)	50.7	47.8		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	14.9

Secondary: Percentage of participants achieving a favorable clinical response at EFU visit in the clinically evaluable (CE) population

End point title	Percentage of participants achieving a favorable clinical response at EFU visit in the clinically evaluable (CE) population

End point description:

Clinical response was defined as "Sustained cure" (All pretherapy signs and symptoms of the index infection have resolved or returned to preinfection status with no evidence of resurgence) AND no additional antibiotic therapy was required for the index infection or "Cure" (All pretherapy signs and symptoms of the index infection have resolved or returned to preinfection status) AND no additional antibiotic therapy was required for the index infection. The percentage of participants with a favorable clinical response at EFU visit in the CE population is presented. MITT population are randomized participants who received at least 1 dose of IV study therapy and had no positive cocci on Gram stain. The CE population was a subset of the MITT population who met criteria for entry into the study, had no significant deviation from the protocol and received the minimum duration of IV study therapy. Only participants with non-missing/non-indeterminate response were assessed at EFU visit.

End point type	Secondary

End point timeframe:

Up to approximately 27 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	82		
Units: Percentage of Participants				
number (not applicable)	64.6	62.2		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	16.8

Secondary: Percentage of participants achieving a favorable clinical response at End of Therapy (EOT) visit in the MITT population

End point title	Percentage of participants achieving a favorable clinical response at End of Therapy (EOT) visit in the MITT population

End point description:

Clinical response was defined as "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 antibiotic therapy was required) or "Cure" (All pretherapy signs and symptoms of the index infection have resolved or returned to preinfection status AND no additional antibiotic therapy was required for the index infection). The percentage of participants achieving a favorable clinical response at EOT visit in the MITT population is presented. MITT population consisting of all randomized participants who received at least 1 dose of IV study therapy and did not have the presence of positive cocci only on baseline Gram stain were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 14 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	136		
Units: Percentage of Participants				
number (not applicable)	71.6	68.4		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	14.3

Secondary: Percentage of participants achieving a favorable clinical response at EOT visit in the clinically evaluable (CE) population

End point title	Percentage of participants achieving a favorable clinical response at EOT visit in the clinically evaluable (CE) population

End point description:

Clinical response was defined as "Sustained cure" (All pretherapy signs and symptoms of the index infection have resolved or returned to preinfection status with no evidence of resurgence) AND no additional antibiotic therapy was required for the index infection or "Cure" (All pretherapy signs and symptoms of the index infection have resolved or returned to preinfection status) AND no additional antibiotic therapy was required for the index infection. The percentage of participants with a favorable clinical response at EOT visit in the CE population is presented. MITT population are randomized participants who received at least 1 dose of IV study therapy and had no positive cocci on Gram stain. The CE population was a subset of the MITT population who met criteria for entry into the study, had no significant deviation from the protocol and received the minimum duration of IV study therapy. Only participants with non-missing/non-indeterminate response were assessed at EOT visit.

End point type	Secondary

End point timeframe:

Up to approximately 14 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	96		
Units: Percentage of Participants				
number (not applicable)	77.4	82.3		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.8
upper limit	6.6

Secondary: Percentage of participants achieving a favorable microbiological response at EOT visit in Microbiological Modified Intent-To-Treat Population (mMITT) population

End point title	Percentage of participants achieving a favorable microbiological response at EOT visit in Microbiological Modified Intent-To-Treat Population (mMITT) population

End point description:

Favorable overall microbiological response rates were defined as "eradication" (A lower respiratory tract culture taken at the EOT visit showed eradication of the pathogen found at study entry) OR "presumed eradication" (No specimen taken because participant was deemed clinically cured or improved) of the baseline pathogen. The percentage of participants achieving a favorable microbiological response at EOT visit in the mMITT population is presented. The MITT population consisted of all randomized participants who received at least 1 dose of IV study therapy and did not have the presence of positive cocci. The microbiological modified intention-to-treat (mMITT) population was a subset of the MITT population that possessed a baseline bacterial pathogen isolated from a lower respiratory tract (LRT) specimen that was identified as the cause of HABP/VABP and against which IMI/REL has been shown to have antibacterial activity.

End point type	Secondary

End point timeframe:

Up to approximately 14 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	73		
Units: Percentage of Participants				
number (not applicable)	57.5	60.3		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	13.1

Secondary: Percentage of participants achieving a favorable microbiological response at EFU visit in microbiological-evaluable (ME) population.

End point title	Percentage of participants achieving a favorable microbiological response at EFU visit in microbiological-evaluable (ME) population.

End point description:

A favorable by-pathogen microbiological response at EFU visit required "eradication" (A lower respiratory tract culture taken at the EFU visit showed eradication of the pathogen found at study entry) or "presumed eradication" (No specimen taken because participant was deemed clinically cured or improved) of the baseline pathogen. The percentage of participants achieving a favorable microbiological response at EFU visit in the ME population is presented. All randomized participants receiving ≥1 dose of IV study therapy without presence of positive cocci (MITT); who met important diagnostic criteria for study with no significant protocol deviation and received minimum duration of IV study therapy (CE); had a baseline bacterial pathogen cause of HABP/VABP against which IMI/REL has antibacterial activity and results from a lower respiratory tract culture obtained at indicated time point (ME); and had non-missing/non-indeterminate response at EFU.

End point type	Secondary

End point timeframe:

Up to approximately 27 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	37		
Units: Percentage of Participants				
number (not applicable)	80.0	78.4		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	19.8

Secondary: Percentage of participants achieving a favorable microbiological response at EOT visit in the ME population

End point title	Percentage of participants achieving a favorable microbiological response at EOT visit in the ME population

End point description:

Favorable overall microbiological response rates was defined as "eradication" (A lower respiratory tract culture taken at the EOT visit showed eradication of the pathogen found at study entry) OR "presumed eradication" (No specimen taken because participant was deemed clinically cured or improved) of the baseline pathogen. The percentage of participants achieving a favorable microbiological response at End of Treatment (EOT) visit in the ME population is presented. All randomized participants receiving ≥1 dose of IV study therapy without presence of positive cocci (MITT); who met important diagnostic criteria for study with no significant protocol deviation and received minimum duration of IV study therapy (CE); had a baseline bacterial pathogen cause of HABP/VABP against which IMI/REL has antibacterial activity and results from a lower respiratory tract culture obtained at indicated time point (ME); and had non-missing/non-indeterminate response at EOT.

End point type	Secondary

End point timeframe:

Up to approximately 14 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	47		
Units: Percentage of Participants				
number (not applicable)	71.9	74.5		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.8
upper limit	14.4

Secondary: Percentage of participants experiencing adverse events (AEs)

End point title	Percentage of participants experiencing adverse events (AEs)

End point description:

An AE was defined as any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The percentage of participants experiencing an AE was reported for each arm. All randomized participants who received at least 1 dose of IV study therapy were assessed.

End point type	Secondary

End point timeframe:

Up to approximately 98 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	136		
Units: Percentage of Participants				
number (not applicable)	86.6	84.6		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	10.6

Secondary: Percentage of participants discontinuing study drug due to AEs

End point title	Percentage of participants discontinuing study drug due to AEs

End point description:

An AE was defined as any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The percentage of participants that discontinued study therapy due to an AE was reported for each arm. All randomized participants who received at least 1 dose of IV study therapy were assessed.

End point type	Secondary

End point timeframe:

Up to approximately 14 days

End point values	IMI/REL FDC	PIP/TAZ FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	136		
Units: Percentage of Participants				
number (not applicable)	3.7	8.1		

Statistical analyses

Statistical analysis title	Adjusted Difference in Percentage
Comparison groups	IMI/REL FDC v PIP/TAZ FDC
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Adjusted difference in percentage
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	1.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 98 days	
Adverse event reporting additional description:	
All-cause mortality: all randomized participants; Safety: all randomized participants who received at least one dose of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	PIP/TAZ
Reporting group description:	
Piperacillin/tazobactam (PIP/TAZ) was administered IV as a FDC at a dosage of 4000 mg PIP/500 mg TAZ once every 6 hours for a minimum 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 methicillin-resistant Staphylococcus aureus (MRSA) is 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:	
Imipenem/cilastatin/relebactam (IMI/REL) administered intravenously (IV) as a fixed-dose combination (FDC) at a dosage of 500 mg IMI/250 mg REL, once every 6 hours for a minimum 7 days, up to 14 days. At the start of IMI/REL treatment, participants will be treated empirically with 600 mg open-label linezolid administered IV every 12 hours until methicillin-resistant Staphylococcus aureus (MRSA) is ruled out. Participants with confirmed MRSA infection will continue 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	21 / 136 (15.44%)	29 / 134 (21.64%)	
number of deaths (all causes)	11	18	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung squamous cell carcinoma stage IV			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic leak			

subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic fistula			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 136 (0.00%)	4 / 134 (2.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Shock			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Shock haemorrhagic			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular tachyarrhythmia			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Basal ganglia haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain stem haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	3 / 136 (2.21%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 136 (0.74%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Mouth ulceration			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastropleural fistula			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	3 / 136 (2.21%)	9 / 134 (6.72%)	
occurrences causally related to treatment / all	0 / 3	1 / 10	
deaths causally related to treatment / all	0 / 2	1 / 5	
Pulmonary embolism			
subjects affected / exposed	1 / 136 (0.74%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pneumothorax			
subjects affected / exposed	2 / 136 (1.47%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mediastinitis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (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 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 136 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 136 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	1 / 136 (0.74%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	2 / 136 (1.47%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Tracheobronchitis			
subjects affected / exposed	0 / 136 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	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	66 / 136 (48.53%)	81 / 134 (60.45%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 136 (9.56%)	12 / 134 (8.96%)	
occurrences (all)	13	12	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 136 (5.15%)	8 / 134 (5.97%)	
occurrences (all)	7	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 136 (12.50%)	18 / 134 (13.43%)	
occurrences (all)	17	20	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 136 (6.62%)	15 / 134 (11.19%)	
occurrences (all)	10	15	
Diarrhoea			
subjects affected / exposed	22 / 136 (16.18%)	21 / 134 (15.67%)	
occurrences (all)	25	27	
Vomiting			
subjects affected / exposed	6 / 136 (4.41%)	8 / 134 (5.97%)	
occurrences (all)	6	11	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	13 / 136 (9.56%)	17 / 134 (12.69%)	
occurrences (all)	13	18	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 136 (2.94%)	8 / 134 (5.97%)	
occurrences (all)	4	8	
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	9 / 136 (6.62%)	17 / 134 (12.69%)	
occurrences (all)	9	18	
Hypokalaemia			
subjects affected / exposed	17 / 136 (12.50%)	13 / 134 (9.70%)	
occurrences (all)	19	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2019	The major changes in Amendment (AM) 1 were changes to the microbiological response definitions at EOT and EFU as well as additional clarifications to procedures in the Schedule of Activities (SOA).
29 October 2019	The main reason for this amendment (AM-02) was to change the upper age limit of participants from ≤75 years to ≤90 years of age due to the unmet medical need for treatment of HABP/VABP in the elderly population.
12 February 2021	The main reason for this amendment (AM-03) was to allow for inclusion of participants with a gram stain result showing 'no organism seen' and to provide clarification for key inclusion/exclusion criteria and study procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported