



Clinical trial results:

Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Urinary Tract Infection

Summary

EudraCT number	2011-005707-32
Trial protocol	ES GR LV BG PL
Global end of trial date	28 July 2015

Results information

Result version number	v2 (current)
This version publication date	17 July 2019
First version publication date	16 July 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	7655-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01505634
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration Number: MK-7655-003

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	28 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2015
Global end of trial reached?	Yes
Global end of trial date	28 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 54
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Latvia: 46
Country: Number of subjects enrolled	Peru: 21
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Romania: 63
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Turkey: 27
Country: Number of subjects enrolled	Ukraine: 59
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	302
EEA total number of subjects	180

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)	180
From 65 to 84 years	117
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were enrolled with complicated urinary tract infection (cUTI) or acute pyelonephritis judged by the investigator to be serious (requiring hospitalization and intravenous (IV) antibiotic therapy); pyuria; and 1 positive urine culture within 48 hours of enrollment.

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, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Relebactam 250 mg with imipenem/cilastatin

Arm description:

Relebactam 250 mg IV co-administered with 500 mg of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Arm type	Experimental
Investigational medicinal product name	Relebactam 250 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Relebactam 250 mg IV co-administered with imipenem/cilastatin 500 mg IV every 6 hours for a minimum of 96 hours

Investigational medicinal product name	imipenem/cilastatin 500 mg
Investigational medicinal product code	
Other name	PRIMAXIN®, TIENAM®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Relebactam 250 mg IV co-administered with imipenem/cilastatin 500 mg IV every 6 hours for a minimum of 96 hours

Investigational medicinal product name	Ciprofloxacin 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg of Ciprofloxacin (as optional oral therapy following minimum duration of IV study drug) twice a day

Arm title	Relebactam 125 mg with imipenem/cilastatin
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Arm description:

Relebactam 125 mg IV co-administered with 500 mg of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Arm type	Experimental
Investigational medicinal product name	imipenem/cilastatin 500 mg
Investigational medicinal product code	
Other name	PRIMAXIN®, TIENAM®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Relebactam 125 mg IV co-administered with imipenem/cilastatin 500 mg IV every 6 hours for a minimum of 96 hours

Investigational medicinal product name	Relebactam 125 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Relebactam 125 mg IV co-administered with imipenem/cilastatin 500 mg IV every 6 hours for a minimum of 96 hours

Investigational medicinal product name	Ciprofloxacin 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg of Ciprofloxacin (as optional oral therapy following minimum duration of IV study drug) twice a day

Arm title	Placebo for relebactam with imipenem/cilastatin
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Arm description:

Matching placebo for relebactam (0.9% normal saline) IV co-administered with 500 mg dose of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Arm type	Placebo
Investigational medicinal product name	imipenem/cilastatin 500 mg
Investigational medicinal product code	
Other name	PRIMAXIN®, TIENAM®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo for relebactam IV co-administered with imipenem/cilastatin 500 mg IV every 6 hours for a minimum of 96 hours

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

Dosage and administration details:

Matching placebo for relebactam IV co-administered with imipenem/cilastatin 500 mg IV every 6 hours for a minimum of 96 hours

Investigational medicinal product name	Ciprofloxacin 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg of Ciprofloxacin (as optional oral therapy following minimum duration of IV study drug) twice a day

Number of subjects in period 1	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin
Started	101	101	100
Treated	99	99	100
Completed	92	91	94
Not completed	9	10	6
Adverse event, serious fatal	1	-	-
In a conflict zone	-	-	1
Consent withdrawn by subject	2	5	1
Physician decision	1	1	-
Adverse event, non-fatal	1	-	-
Insufficient supply of drug at site	1	-	-
Lost to follow-up	1	4	4
Protocol deviation	2	-	-

Baseline characteristics

Reporting groups

Reporting group title	Relebactam 250 mg with imipenem/cilastatin
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Reporting group description:

Relebactam 250 mg IV co-administered with 500 mg of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Reporting group title	Relebactam 125 mg with imipenem/cilastatin
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Reporting group description:

Relebactam 125 mg IV co-administered with 500 mg of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Reporting group title	Placebo for relebactam with imipenem/cilastatin
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Reporting group description:

Matching placebo for relebactam (0.9% normal saline) IV co-administered with 500 mg dose of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Reporting group values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin
Number of subjects	101	101	100
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)	59	64	57
From 65-84 years	39	37	41
85 years and over	3	0	2
Age Continuous Units: years			
arithmetic mean	57.9	55.9	55.7
standard deviation	± 17.3	± 17.5	± 19.2
Gender Categorical Units: Subjects			
Female	51	60	42
Male	50	41	58

Reporting group values	Total		
Number of subjects	302		

Age Categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	180		
From 65-84 years	117		
85 years and over	5		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical			
Units: Subjects			
Female	153		
Male	149		

End points

End points reporting groups

Reporting group title	Relebactam 250 mg with imipenem/cilastatin
Reporting group description: Relebactam 250 mg IV co-administered with 500 mg of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.	
Reporting group title	Relebactam 125 mg with imipenem/cilastatin
Reporting group description: Relebactam 125 mg IV co-administered with 500 mg of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.	
Reporting group title	Placebo for relebactam with imipenem/cilastatin
Reporting group description: Matching placebo for relebactam (0.9% normal saline) IV co-administered with 500 mg dose of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.	

Primary: Percentage of Participants with a Favorable Microbiological Response at Completion of IV Study Therapy

End point title	Percentage of Participants with a Favorable Microbiological Response at Completion of IV Study Therapy
End point description: Microbiological response (MR) was assessed based on results of bacterial cultures obtained at completion of IV study medication relative to cultures obtained at baseline. A favorable microbiological response was defined as eradication of all pathogens identified at baseline. Microbiological response was assessed separately for each participant and pathogen identified in the Microbiologically Evaluable (ME) population that included participants with a urine culture confirmed to be positive for at least 1 gram-negative and/or anaerobic pathogen(s) commonly isolated in UTI. The overall microbiological response was determined as "favorable" if all pathogens isolated from a participant at baseline demonstrated a "favorable" response (eradication) at the time point evaluated. The analysis included all participants in the ME population with non-missing/non-indeterminate response.	
End point type	Primary
End point timeframe: At time of last dose of IV study medication (up to post-randomization day 14)	

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	71	75	
Units: Percentage of Participants				
number (confidence interval 95%)	95.5 (87.5 to 99.1)	98.6 (92.4 to 100.0)	98.7 (92.8 to 100.0)	

Statistical analyses

Statistical analysis title	Percent Difference (Diff) in Favorable MR
Statistical analysis description: Non-inferiority for the relebactam 250 mg + imipenem/cilastatin group versus the Placebo for relebactam + imipenem/cilastatin group was demonstrated if the lower bound of the 95% CI was not lower than the pre-specified non-inferiority margin of -15%.	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.005
Method	Miettinen and Nurminen Method
Parameter estimate	Percent Difference
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	3.2

Statistical analysis title	Percent Diff in Favorable MR
Statistical analysis description: Non-inferiority for the relebactam 125 mg + imipenem/cilastatin group versus the Placebo for relebactam + imipenem/cilastatin group was demonstrated if the lower bound of the 95% CI was not lower than the pre-specified non-inferiority margin of -15%.	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen Method
Parameter estimate	Percent Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	5.9

Primary: Percentage of Participants with an Elevated Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) Laboratory Value That Was \geq 5X the Upper Limit of Normal (ULN)

End point title	Percentage of Participants with an Elevated Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) Laboratory Value That Was \geq 5X the Upper Limit of Normal (ULN)
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End point description:

All randomized participants who received ≥ 1 dose of study treatment had AST and ALT levels measured up to 14 days following completion of all study medication. Participants who had 2 confirmed elevations of either AST or ALT that were 5X ULN or greater were recorded.

End point type	Primary
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End point timeframe:

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

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants	1	1	0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of ECI #1
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Statistical analysis description:

Event of Clinical Interest (ECI) #1 is a confirmed elevated AST or ALT $\geq 5X$ ULN. Inferential testing for statistical significance with p-values and 95% confidence intervals was performed to provide a comparison between the relebactam 250 mg + imipenem/cilastatin group versus the Placebo for relebactam + imipenem/cilastatin group.

Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.315
Method	Miettinen and Nurminen Method
Parameter estimate	Percent Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	5.5

Statistical analysis title	Percent Diff in Number of ECI #1
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Statistical analysis description:

Event of Clinical Interest (ECI) #1 is a confirmed elevated AST or ALT $\geq 5X$ ULN. Inferential testing for statistical significance with p-values and 95% confidence intervals was performed to provide a comparison between the relebactam 125 mg + imipenem/cilastatin group versus the Placebo for relebactam + imipenem/cilastatin group.

Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.315
Method	Miettinen and Nurminen Method
Parameter estimate	Percent Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	5.5

Primary: Percentage of Participants with Elevated AST or ALT Laboratory Values That Were $\geq 3X$ the ULN, as Well as Elevated Total Bilirubin $\geq 2X$ the ULN, and Alkaline Phosphatase Values $< 2X$ the ULN

End point title	Percentage of Participants with Elevated AST or ALT Laboratory Values That Were $\geq 3X$ the ULN, as Well as Elevated Total Bilirubin $\geq 2X$ the ULN, and Alkaline Phosphatase Values $< 2X$ the ULN
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End point description:

All randomized participants who received ≥ 1 dose of study treatment had AST, ALT, total bilirubin, and Alkaline Phosphatase (ALP) levels measured up to 14 days following completion of all study medication. Participants who had elevations of AST or ALT that were $\geq 3X$ ULN, total bilirubin measurements that were $\geq 2X$ ULN and, at the same time, an ALP measurement of $< 2X$ ULN were recorded.

End point type	Primary
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End point timeframe:

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

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants	0	0	0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of ECI #2
Statistical analysis description:	
Event of Clinical Interest (ECI) #2 is elevated AST or ALT $\geq 3X$ ULN, elevated total bilirubin $\geq 2X$ ULN, and with an ALP $< 2X$ ULN. Inferential testing for statistical significance with p-values and 95% confidence intervals was performed to provide a comparison between the relebactam 250 mg + imipenem/cilastatin group versus the Placebo for relebactam + imipenem/cilastatin group.	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	> 0.999
Method	Miettinen and Nurminen Method
Parameter estimate	Percent Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	3.8

Notes:

[1] - There were no participants who met the criteria for ECI #2.

Statistical analysis title	Percent Diff in Number of ECI #2
Statistical analysis description:	
Event of Clinical Interest (ECI) #2 is elevated AST or ALT $\geq 3X$ ULN, elevated total bilirubin $\geq 2X$ ULN, and with an ALP $< 2X$ ULN. Inferential testing for statistical significance with p-values and 95% confidence intervals was performed to provide a comparison between the relebactam 125 mg + imipenem/cilastatin group versus the Placebo for relebactam + imipenem/cilastatin group.	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	> 0.999
Method	Miettinen and Nurminen Method
Parameter estimate	Percent Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	3.8

Notes:

[2] - There were no participants who met the criteria for ECI #2.

Primary: Percentage of Participants with At Least 1 Adverse Event (AE)

End point title	Percentage of Participants with At Least 1 Adverse Event (AE)
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End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to

the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE. The population analyzed was all randomized participants who received ≥ 1 dose of study treatment.

End point type	Primary
End point timeframe:	
Up to 14 days following completion of all study medication (up to 28 days)	

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants				
number (not applicable)	28.3	29.3	30.0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of AEs
Statistical analysis description:	
Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.3
upper limit	10.9

Statistical analysis title	Percent Diff in Number of AEs
Statistical analysis description:	
Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	12

Primary: Percentage of Participants with Any Serious Adverse Event (SAE)

End point title	Percentage of Participants with Any Serious Adverse Event (SAE)
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End point description:

SAEs were collected on all randomized participants who received ≥ 1 dose of study treatment. A SAE was an AE that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged an existing inpatient hospitalization, was a congenital anomaly/birth defect, was a cancer, was associated with an overdose, was another important medical event. The population analyzed was all randomized participants who received ≥ 1 dose of study treatment.

End point type	Primary
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End point timeframe:

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

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants				
number (not applicable)	3.0	1.0	3.0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of SAEs
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Statistical analysis description:

Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.

Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
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Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	5.9

Statistical analysis title	Percent Diff in Number of SAEs
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	2.8

Primary: Percentage of Participants with Any Drug-related AE	
End point title	Percentage of Participants with Any Drug-related AE
End point description: An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE. A drug-related AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product that the investigator determined to be possibly, probably, or definitely related to the treatment. The population analyzed was all randomized participants who received ≥ 1 dose of study treatment.	
End point type	Primary
End point timeframe: Up to 14 days following completion of all study medication (up to 28 days)	

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants				
number (not applicable)	10.1	9.1	9.0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of DR AEs
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	9.8

Statistical analysis title	Percent Diff in Number of DR AEs
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	8.6

Primary: Percentage of Participants with Drug-related Serious AEs

End point title	Percentage of Participants with Drug-related Serious AEs
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End point description:

Drug-related SAEs were collected on all randomized participants who received ≥ 1 dose of study treatment. A serious, drug-related AE was an AE that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged an existing inpatient hospitalization, was a congenital anomaly/birth defect, was a cancer, was associated with an overdose, was another important medical event. The SAE was determined to be possibly, probably, or definitely related to the treatment by the investigator. The population analyzed was all randomized participants who received ≥ 1 dose of study treatment.

End point type	Primary
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End point timeframe:

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

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants				
number (not applicable)	1.0	0	1.0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of DR SAEs
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Statistical analysis description:

Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method

Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	4.6

Statistical analysis title	Percent Diff in Number of DR SAEs
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Statistical analysis description:

Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method

Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	2.8

Primary: Percentage of Participants Who Discontinued IV Study Therapy Due to an AE

End point title	Percentage of Participants Who Discontinued IV Study Therapy Due to an AE
End point description:	
An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE. The population analyzed was all randomized participants who received ≥ 1 dose of study treatment.	
End point type	Primary
End point timeframe:	
Up to 14 days	

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants				
number (not applicable)	3.0	1.0	2.0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of Discons Due to AEs
Statistical analysis description:	
Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	6.8

Statistical analysis title	Percent Diff in Number of Discons Due to AEs
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	3.7

Primary: Percentage of Participants Who Discontinued IV Study Therapy Due to a Drug-related AE

End point title	Percentage of Participants Who Discontinued IV Study Therapy Due to a Drug-related AE
End point description: An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE. A drug-related AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product that the investigator determined to be possibly, probably, or definitely related to the treatment. The population analyzed was all randomized participants who received ≥ 1 dose of study treatment.	
End point type	Primary
End point timeframe: Up to 14 days	

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants				
number (not applicable)	2.0	1.0	1.0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of Discons Due to DR AEs
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	6.2

Statistical analysis title	Percent Diff in Number of Discons Due to DR AEs
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	4.6

Primary: Percentage of participants with specific AEs with incidence of ≥ 4 participants in one treatment group

End point title	Percentage of participants with specific AEs with incidence of ≥ 4 participants in one treatment group
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End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE. Analysis includes specific adverse events with an incidence of ≥ 4 participants in one treatment group or system organ class. The population analyzed was all randomized participants who received ≥ 1 dose of study treatment.

End point type	Primary
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End point timeframe:

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

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99	99	100	
Units: Percentage of Participants				
number (not applicable)				
Diarrhoea	5.1	2.0	4.0	
Nausea	4.0	6.1	4.0	
Bacteriuria	1.0	2.0	4.0	
White blood cells (WBC) urine positive	1.0	1.0	4.0	
Headache	7.1	3.0	4.0	

Statistical analyses

Statistical analysis title	Percent Diff in Number of AEs: Diarrhoea
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Statistical analysis description:

Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.

Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	7.8

Statistical analysis title	Percent Diff in Number of AEs: Diarrhoea
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	3.6

Statistical analysis title	Percent Diff in Number of AEs: Nausea
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	6.5

Statistical analysis title	Percent Diff in Number of AEs: Nausea
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	9.2

Statistical analysis title	Percent Diff in Number of AEs: Bacteriuria
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	1.9

Statistical analysis title	Percent Diff in Number of AEs: Bacteriuria
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	3.6

Statistical analysis title	Percent Diff in Number of AEs: WBC urine positive
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	1.9

Statistical analysis title	Percent Diff in Number of AEs: WBC urine positive
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	1.9

Statistical analysis title	Percent Diff in Number of AEs: Headache
Statistical analysis description: Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.	
Comparison groups	Relebactam 250 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	3.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	10.4

Statistical analysis title	Percent Diff in Number of AEs: Headache
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Statistical analysis description:

Difference in percentage and 95% CI are based on unconditional and asymptotic Miettinen and Nurminen method.

Comparison groups	Relebactam 125 mg with imipenem/cilastatin v Placebo for relebactam with imipenem/cilastatin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percent Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	5.1

Secondary: Percentage of Participants with a Favorable Microbiological Response at Completion of IV Study Therapy Who Have Imipenem-resistant, Gram-negative cUTI Infections

End point title	Percentage of Participants with a Favorable Microbiological Response at Completion of IV Study Therapy Who Have Imipenem-resistant, Gram-negative cUTI Infections
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End point description:

Microbiological response was assessed based on results of bacterial cultures obtained at completion of IV study medication relative to cultures obtained at baseline. A favorable microbiological response was defined as eradication of all pathogens identified at baseline. Microbiological response was assessed separately for each participant and pathogen identified in the Microbiologically Evaluable (ME) population that included participants with a urine culture confirmed to be positive for imipenem-resistant gram-negative or anaerobic infections at baseline. The overall microbiological response was determined as "favorable" if all pathogens isolated from a participant at baseline demonstrated a "favorable" response (eradication) at the time point evaluated. The analysis included all participants in the ME population with imipenem-resistant gram-negative infections at baseline.

End point type	Secondary
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End point timeframe:

At time of last dose of IV study medication (up to post-randomization day 14)

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	7	6	
Units: Percentage of Participants				
number (confidence interval 95%)	100.0 (69.2 to 100.0)	100.0 (59.0 to 100.0)	100.0 (54.1 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Favorable Microbiological Response at Early Follow-up

End point title	Percentage of Participants with a Favorable Microbiological Response at Early Follow-up
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End point description:

Microbiological response was assessed based on results of bacterial cultures obtained up to 9 days following completion of all study medication (IV and oral) relative to cultures obtained at baseline. A favorable microbiological response was defined as eradication of all pathogens identified at baseline. Microbiological response was assessed separately for each participant and pathogen identified in the Microbiologically Evaluable (ME) population that included participants with a urine culture confirmed to be positive for at least 1 gram-negative and/or anaerobic pathogen(s) commonly isolated in UTI. The overall microbiological response was determined as "favorable" if all pathogens isolated from a participant at baseline demonstrated a "favorable" response (eradication) at the time point evaluated. The analysis included all participants in the ME population with non-missing/non-indeterminate response.

End point type	Secondary
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End point timeframe:

Up to 9 days following completion of all IV and oral study medication (up to Day 23)

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65	72	71	
Units: Percentage of Participants				
number (confidence interval 95%)	61.5 (48.6 to 73.3)	68.1 (56.0 to 78.6)	70.4 (58.4 to 80.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Favorable Clinical Response at

Completion of IV Study Therapy

End point title	Percentage of Participants with a Favorable Clinical Response at Completion of IV Study Therapy
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End point description:

Clinical response was assessed as favorable (cured or improved) or unfavorable (failure) relative to baseline. Response determination was based on physical findings including fever (or history of fever), chills or rigors (accompanied by fever), flank pain, costovertebral angle tenderness, dysuria, urinary urgency, urinary frequency, suprapubic or pelvic pain, nausea, or vomiting. Clinical response was assessed in the Microbiologically Evaluable (ME) population that included participants with a urine culture confirmed to be positive for at least 1 gram-negative and/or anaerobic pathogen(s) commonly isolated in UTI. The analysis included all participants in the ME population with non-missing/non-indeterminate response.

End point type	Secondary
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End point timeframe:

At time of last dose of IV study medication (up to post-randomization day 14)

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	78	80	
Units: Percentage of Participants				
number (confidence interval 95%)	97.1 (89.9 to 99.6)	98.7 (93.1 to 100.0)	98.8 (93.2 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Favorable Clinical Response at Early Follow-up

End point title	Percentage of Participants with a Favorable Clinical Response at Early Follow-up
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End point description:

Clinical response was assessed as favorable (cured or improved) or unfavorable (failure) relative to baseline. Response determination was based on physical findings including fever (or history of fever), chills or rigors (accompanied by fever), flank pain, costovertebral angle tenderness, dysuria, urinary urgency, urinary frequency, suprapubic or pelvic pain, nausea, or vomiting. Clinical response was assessed in the Microbiologically Evaluable (ME) population that included participants with a urine culture confirmed to be positive for at least 1 gram-negative and/or anaerobic pathogen(s) commonly isolated in UTI. The analysis included all participants in the ME population with non-missing/non-indeterminate response.

End point type	Secondary
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End point timeframe:

Up to 9 days following completion of all IV and oral study medication (up to Day 23)

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	73	76	
Units: Percentage of Participants				
number (confidence interval 95%)	89.1 (78.8 to 95.5)	91.8 (83.0 to 96.9)	93.4 (85.3 to 97.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Favorable Clinical Response at Late Follow-up

End point title	Percentage of Participants with a Favorable Clinical Response at Late Follow-up
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End point description:

Clinical response was assessed as favorable (cured or improved) or unfavorable (failure) relative to baseline. Response determination was based on physical findings including fever (or history of fever), chills or rigors (accompanied by fever), flank pain, costovertebral angle tenderness, dysuria, urinary urgency, urinary frequency, suprapubic or pelvic pain, nausea, or vomiting. Clinical response was assessed in the Microbiologically Evaluable (ME) population that included participants with a urine culture confirmed to be positive for at least 1 gram-negative and/or anaerobic pathogen(s) commonly isolated in UTI. The analysis included all participants in the ME population with non-missing/non-indeterminate response.

End point type	Secondary
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End point timeframe:

Up to 42 days following completion of all IV and oral study medication (up to Day 56)

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	71	76	
Units: Percentage of Participants				
number (confidence interval 95%)	88.7 (78.1 to 95.3)	87.3 (77.3 to 94.0)	88.2 (78.7 to 94.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Favorable Microbiological Response at Late Follow-up

End point title	Percentage of Participants with a Favorable Microbiological Response at Late Follow-up
End point description:	
Microbiological response was assessed based on results of bacterial cultures obtained up to 42 days following completion of all study medication (IV and oral) relative to cultures obtained at baseline. A favorable microbiological response was defined as eradication of all pathogens identified at baseline. Microbiological response was assessed separately for each participant and pathogen identified in the Microbiologically Evaluable (ME) population that included participants with a urine culture confirmed to be positive for at least 1 gram-negative and/or anaerobic pathogen(s) commonly isolated in UTI. The overall microbiological response was determined as "favorable" if all pathogens isolated from a participant at baseline demonstrated a "favorable" response at the time point evaluated. The analysis included all participants in the ME population with non-missing/non-indeterminate response.	
End point type	Secondary
End point timeframe:	
Up to 42 days following completion of all IV and oral study medication (up to Day 56)	

End point values	Relebactam 250 mg with imipenem/cilastatin	Relebactam 125 mg with imipenem/cilastatin	Placebo for relebactam with imipenem/cilastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	69	72	
Units: Percentage of Participants				
number (confidence interval 95%)	68.3 (55.3 to 79.4)	65.2 (52.8 to 76.3)	62.5 (50.3 to 73.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 42 days following completion of all study therapy for drug-related serious adverse events (up to 56 days); and up to 14 days following completion of all study therapy for all-cause serious and non-serious adverse events (up to 28 days).

Adverse event reporting additional description:

AEs were reported for the All Participants as Treated Population that included all randomized participants who received ≥ 1 dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Relebactam 250 mg + imipenem/cilastatin
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Reporting group description:

Relebactam 250 mg IV co-administered with 500 mg of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Reporting group title	Placebo + imipenem/cilastatin
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Reporting group description:

Matching placebo for relebactam (0.9% normal saline) IV co-administered with 500 mg dose of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Reporting group title	Relebactam 125 mg + imipenem/cilastatin
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Reporting group description:

Relebactam 125 mg IV co-administered with 500 mg of imipenem/cilastatin once every 6 hours for a minimum of 96 hours. After 96 hours of IV treatment, participants may be switched to 500 mg ciprofloxacin (as optional oral therapy following minimum duration of IV study drug), administered orally, twice daily for the remainder of the study. Antibiotic therapy (IV and oral combined) should not exceed 14 days.

Serious adverse events	Relebactam 250 mg + imipenem/cilastatin	Placebo + imipenem/cilastatin	Relebactam 125 mg + imipenem/cilastatin
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 99 (5.05%)	3 / 100 (3.00%)	2 / 99 (2.02%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer			
subjects affected / exposed	1 / 99 (1.01%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Renal neoplasm			
subjects affected / exposed	1 / 99 (1.01%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	0 / 99 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 99 (1.01%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 99 (1.01%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 99 (1.01%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	1 / 99 (1.01%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 99 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Glomerulonephritis rapidly progressive			

subjects affected / exposed	0 / 99 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Peritonitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 99 (1.01%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Relebactam 250 mg + imipenem/cilastatin	Placebo + imipenem/cilastatin	Relebactam 125 mg + imipenem/cilastatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 99 (11.11%)	7 / 100 (7.00%)	9 / 99 (9.09%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 99 (7.07%)	4 / 100 (4.00%)	3 / 99 (3.03%)
occurrences (all)	7	4	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 99 (4.04%)	4 / 100 (4.00%)	6 / 99 (6.06%)
occurrences (all)	4	5	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2012	Protocol Amendment 3 modified the initial inclusion criterion that allowed for inclusion of patients in the study with risk factors for infection with an antibacterial-resistant organism. Additional risk factors for inclusion of these patients were added in this amendment.
13 May 2014	Protocol Amendment 5 removed the inclusion criteria that allowed for participants in the study based on at least one of three risk factors for infection with an antibacterial-resistant organism.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported