Clinical trial results:
A Phase 3, Multi-Center, Randomized, Double-Blind, Double-Dummy Study to Evaluate The Efficacy, Safety, and Tolerability of Carbavance™ (Meropenem/RPX7009) Compared to Piperacillin/Tazobactam in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, in Adults

Summary

EudraCT number	2014-000545-78
Trial protocol	HU CZ SK IT ES PL SI BG GR
Global end of trial date	28 April 2016

Results information

Result version number	v1 (current)
This version publication date	08 June 2017
First version publication date	08 June 2017

Trial information

Trial identification

Sponsor protocol code	Rempex-505

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02166476
WHO universal trial number (UTN)	-
Other trial identifiers	US-IND # : 120040

Notes:

Sponsors

Sponsor organisation name	Rempex Pharmaceuticals, Inc.
Sponsor organisation address	3013 Science Park Rd, 1st Floor, San Diego, United States,
Public contact	Elizabeth Morgan, Rempex Pharmaceuticals Inc., +1 8588756671, liz.morgan@themedco.com
Scientific contact	Jeffery Loutit, Rempex Pharmaceuticals Inc., +1 8588756665, jeff.loutit@THEMEDCO.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 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 April 2016
Global end of trial reached?	Yes
Global end of trial date	28 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of meropenem/RPX7009 (meropenem/vaborbactam) administered by intravenous (IV) infusion in participants with complicated urinary tract infections (cUTIs) or acute pyelonephritis (AP);

To assess the safety and tolerability of meropenem/vaborbactam administered by IV infusion in participants with cUTI or AP; and

To assess the population pharmacokinetics (PK) of meropenem/vaborbactam in participants with cUTI or AP.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belarus: 74
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Peru: 18
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Ukraine: 213
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Romania: 35
Country: Number of subjects enrolled	Slovakia: 31
Country: Number of subjects enrolled	Slovenia: 6
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Bulgaria: 46
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	Greece: 41

Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	550
EEA total number of subjects	205

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)	359
From 65 to 84 years	174
85 years and over	17

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening procedures were performed up to 24 hours prior to the first dose of study drug. All screening procedures were completed prior to randomization and the first dose of study drug.

Period 1

Period 1 title	Rempex-505 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

The investigator, site personnel, Sponsor, and Sponsor's designees involved in monitoring, data management, medical review, and other study aspects were blinded. Only the site pharmacist/qualified designee was unblinded to treatment assignment to allow study drug preparation. The study drug supply was not blinded. The Sponsor and Sponsor's designee involved in monitoring the pharmacy data were also unblinded. This monitor was independent from the primary monitor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Meropenem/Vaborbactam

Arm description:

Meropenem/vaborbactam (meropenem 2 grams [g] plus vaborbactam 2 g), infused in 250 milliliters (mL) normal saline, administered IV over 3 hours, every 8 hours (q8h), with 100 mL saline administered over 30 minutes q8h. Levofloxacin tablets administered orally as a 500-milligram (mg) dose every 24 hours (q24h) after a minimum of 15 doses of IV meropenem/vaborbactam plus saline, if clinically indicated. Total treatment was 10 days, unless a participant had baseline bacteremia where up to 14 days of IV therapy could be administered.

Arm type	Experimental
Investigational medicinal product name	Meropenem/Vaborbactam
Investigational medicinal product code	
Other name	Meropenem/RPX7009, Meropenem 2 g-Vaborbactam 2 g , Carbavance
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants in the meropenem/vaborbactam group received the following infusions q8h: meropenem/vaborbactam diluted in normal saline to a volume of 250 mL and infused over 3 hours and, to preserve the blind, 100 mL normal saline infused over 30 minutes.

Investigational medicinal product name	Levofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

If it was deemed clinically indicated and the participant had received a minimum of 15 doses of study drug, levofloxacin (500 mg) was administered orally q24h as a tablet(s).

Arm title	Piperacillin/Tazobactam

Arm description:

Piperacillin/tazobactam (piperacillin 4 g plus tazobactam 0.5 g), infused in 100 mL normal saline, administered IV over 30 minutes, q8h, with 250 mL saline administered over 30 minutes q8h.

Levofloxacin tablets administered orally as a 500-mg dose q24h after a minimum of 15 doses of IV piperacillin/tazobactam plus saline, if clinically indicated. Total treatment was 10 days, unless a participant had baseline bacteremia where up to 14 days of IV therapy could be administered.

Arm type	Active comparator
Investigational medicinal product name	Piperacillin/Tazobactam
Investigational medicinal product code	
Other name	Piperacillin 4 g-Tazobactam 0.5 g
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants in the piperacillin/tazobactam group received the following infusions q8h: piperacillin/tazobactam 4.5 g (piperacillin 4 g-tazobactam 0.5 g) diluted in normal saline to a volume of 100 mL and infused over 30 minutes and, to preserve the blind, 250 mL normal saline infused over 3 hours.

Investigational medicinal product name	Levofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

If it was deemed clinically indicated and the participant had received a minimum of 15 doses of study drug, levofloxacin (500 mg) was administered orally q24h as a tablet(s).

Number of subjects in period 1[1]	Meropenem/Vaborbactam	Piperacillin/Tazobactam
Started	272	273
Received at Least 1 Dose of Study Drug	272	273
Not Completed	14 [2]	23 [3]
Completed	258	250
Not completed	14	23
Unable to come for a visit	-	3
Consent withdrawn by subject	5	7
Physician decision	1	-
Adverse event	3	3
Lost to follow-up	5	10

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Between the 2 Arms, 5 participants were randomized but never dosed: 4 participants withdrew consent and 1 participant did not meet the inclusion criteria and as such, was ineligible to be dosed.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Between the 2 Arms, 5 participants were randomized but never dosed: 4 participants withdrew consent and 1 participant did not meet the inclusion criteria and as such, was ineligible to be dosed.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.

Justification: Between the 2 Arms, 5 participants were randomized but never dosed: 4 participants withdrew consent and 1 participant did not meet the inclusion criteria and as such, was ineligible to be dosed.

Baseline characteristics

Reporting groups	
Reporting group title	Meropenem/Vaborbactam
Reporting group description:	
Meropenem/vaborbactam (meropenem 2 grams [g] plus vaborbactam 2 g), infused in 250 milliliters (mL) normal saline, administered IV over 3 hours, every 8 hours (q8h), with 100 mL saline administered over 30 minutes q8h. Levofloxacin tablets administered orally as a 500-milligram (mg) dose every 24 hours (q24h) after a minimum of 15 doses of IV meropenem/vaborbactam plus saline, if clinically indicated. Total treatment was 10 days, unless a participant had baseline bacteremia where up to 14 days of IV therapy could be administered.	
Reporting group title	Piperacillin/Tazobactam
Reporting group description:	
Piperacillin/tazobactam (piperacillin 4 g plus tazobactam 0.5 g), infused in 100 mL normal saline, administered IV over 30 minutes, q8h, with 250 mL saline administered over 30 minutes q8h. Levofloxacin tablets administered orally as a 500-mg dose q24h after a minimum of 15 doses of IV piperacillin/tazobactam plus saline, if clinically indicated. Total treatment was 10 days, unless a participant had baseline bacteremia where up to 14 days of IV therapy could be administered.	

Reporting group values	Meropenem/Vaborbactam	Piperacillin/Tazobactam	Total
Number of subjects	272	273	545
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)	185	170	355
From 65-84 years	79	94	173
85 years and over	8	9	17
Age continuous Units: years			
arithmetic mean	53	52.6	
standard deviation	± 19.42	± 20.93	-
Gender categorical Units: Subjects			
Female	181	180	361
Male	91	93	184
Ethnicity Units: Subjects			
Hispanic or Latino	24	19	43
Not Hispanic or Latino	248	254	502
Race Units: Subjects			
Asian	5	5	10
Black or African American	3	4	7
White	254	252	506
More than one race	10	12	22

End points

End points reporting groups

Reporting group title	Meropenem/Vaborbactam

Reporting group description:

Meropenem/vaborbactam (meropenem 2 grams [g] plus vaborbactam 2 g), infused in 250 milliliters (mL) normal saline, administered IV over 3 hours, every 8 hours (q8h), with 100 mL saline administered over 30 minutes q8h. Levofloxacin tablets administered orally as a 500-milligram (mg) dose every 24 hours (q24h) after a minimum of 15 doses of IV meropenem/vaborbactam plus saline, if clinically indicated. Total treatment was 10 days, unless a participant had baseline bacteremia where up to 14 days of IV therapy could be administered.

Reporting group title	Piperacillin/Tazobactam

Reporting group description:

Piperacillin/tazobactam (piperacillin 4 g plus tazobactam 0.5 g), infused in 100 mL normal saline, administered IV over 30 minutes, q8h, with 250 mL saline administered over 30 minutes q8h. Levofloxacin tablets administered orally as a 500-mg dose q24h after a minimum of 15 doses of IV piperacillin/tazobactam plus saline, if clinically indicated. Total treatment was 10 days, unless a participant had baseline bacteremia where up to 14 days of IV therapy could be administered.

Subject analysis set title	Microbiological Modified Intent-To-Treat (m-MITT) Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The m-MITT Population included all participants who met the modified intent-to-treat (MITT) criteria (screened, randomized, and received at least 1 dose of study drug) and had a baseline bacterial pathogen(s) of ≥10^5 colony-forming units (CFU)/mL of urine at baseline urine culture or the same bacterial pathogen present in concurrent blood and urine cultures.

Subject analysis set title	Microbiological Evaluable (ME) Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The ME Population included all participants who met MITT criteria and all of the following criteria: a bacterial pathogen(s) of ≥10^5 CFU/mL of urine at baseline urine culture for evaluation or have the same bacterial pathogen present in concurrent blood and urine cultures; no key inclusion or exclusion violations; a clinical outcome (Cure, Improvement, or Failure) and microbiologic outcome (eradication or persistence) at end of intravenous treatment (EOIVT), unless criteria for Failure on clinical outcome were met at an earlier time point; received ≥80% or ≤120% of expected IV doses; missed no more than 1 IV dose in the first 48 hours, missed no more than 2 consecutive IV doses; received no less than 6 doses for failure or no less than 9 doses for cure; only had an identified gram-positive pathogen in the urine and had received >48 hours of an antibiotic, with only gram-positive coverage not included in the m-MITT Population.

Subject analysis set title	Clinical Evaluable (CE) Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The CE Population includes participants who meet the MITT criteria (screened, randomized, and received at least 1 dose of study drug), as well as the following criteria: have no key inclusion or exclusion violations; obtained a clinical outcome (Cure, Improvement, or Failure) at EOIVT, unless criteria for Failure on clinical outcome were met at an earlier time point; received ≥80% and ≤120% of expected IV doses for the completed treatment duration, missed no more than 1 IV dose in the first 48 hours of treatment, and missed no more than 2 consecutive IV doses overall; received ≥6 doses of study drug if classified as a Failure on clinical outcome, or received ≥9 doses of study drug if classified as a Cure on clinical outcome. These criteria were reviewed to identify which participants should be excluded from the CE Population prior to unblinding.

Subject analysis set title	PK Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK Population included participants in the MITT Population (only participants screened and randomized to study drug [meropenem/vaborbactam] and those who received at least 1 dose of study drug) and had at least 1 plasma PK sample drawn. Due to renal impairment, 28 participants received a reduced dose of the study drug (meropenem 1 g plus vaborbactam 1 g).

Subject analysis set title	m-MITT by Pathogen
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Analysis by pathogen in the m-MITT Population using both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) microbiologic outcome criteria at Day 3, EOIVT (Days 5-14), end of treatment (EOT) (Days 10-14), test of cure (TOC) (Days 15-23), and late follow-up (LFU) (Days 22- 30).

Pathogens: Enterobacter cloacae (E. cloacae); Enterococcus faecalis (E. faecalis); Escherichia coli (E. coli); Klebsiella pneumoniae (K. pneumoniae)

Subject analysis set title	ME by Pathogen
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Analysis by pathogen in the ME Population using both the FDA and EMA microbiologic outcome criteria at Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22- 30).

Pathogens: E. cloacae; E. faecalis; E. coli; K. pneumoniae

Primary: Proportion Of Participants In The m-MITT Population Who Achieved Overall Success At The EOIVT Visit

End point title	Proportion Of Participants In The m-MITT Population Who Achieved Overall Success At The EOIVT Visit

End point description:

This was the primary outcome measure for the FDA. For this composite outcome measure, overall success was achieved with a clinical outcome of Cure or Improvement and microbiologic outcome of Eradication at EOIVT. Cure was defined as the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP. Improvement was defined as lessening, incomplete resolution, or no worsening of the baseline signs and symptoms of cUTI or AP, but continued IV therapy was warranted. Eradication was defined using the FDA's CFU/mL criteria that the bacterial pathogen(s) found at baseline was/were reduced to <10^4 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Primary

End point timeframe:

EOIVT (Days 5-14)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	182		
Units: Participants	189	171		

Statistical analyses

Statistical analysis title	m-MITT and Overall Success

Statistical analysis description:

Treatment difference is the estimate of the difference in the overall success rate between the 2 treatment arms. The difference estimates and the 95% confidence interval (CI) are obtained based on Miettinen and Nurminen method.

Comparison groups	Meropenem/Vaborbactam v Piperacillin/Tazobactam

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Treatment Difference
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	9.1

Notes:

[1] - The non-inferiority margin was a difference of 15%. Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the treatment difference for overall success at EOIVT was ≥-15%.

Primary: Proportion Of Participants In The m-MITT Population Who Achieved A Microbiologic Outcome Of Eradication At The TOC Visit

End point title	Proportion Of Participants In The m-MITT Population Who Achieved A Microbiologic Outcome Of Eradication At The TOC Visit

End point description:

This was the primary outcome measure for the EMA. For this measure, a microbiologic outcome of Eradication was defined using the EMA's CFU/mL criteria: bacterial pathogen(s) found at baseline was/were reduced to <10^3 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Primary

End point timeframe:

TOC (Days 15-23)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	182		
Units: Participants	128	105		

Statistical analyses

Statistical analysis title	m-MITT and Eradication

Statistical analysis description:

Treatment difference is the estimate of the difference in the Eradication rate between the 2 treatment arms. The difference estimates and the 95% CIs are obtained based on Miettinen and Nurminen method.

Comparison groups	Meropenem/Vaborbactam v Piperacillin/Tazobactam
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Treatment Difference
Point estimate	9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	18.7

Notes:

[2] - The noninferiority margin was a difference of 15%. Meropenem/vaborbactam was claimed to be noninferior only if noninferiority was demonstrated for microbial eradication at TOC in the m-MITT Population.

Primary: Proportion Of Participants In The ME Population Who Achieved A Microbiologic Outcome Of Eradication

End point title	Proportion Of Participants In The ME Population Who Achieved A Microbiologic Outcome Of Eradication

End point description:

This was the primary outcome measure for the EMA. For this measure, a microbiologic outcome of Eradication was defined using the EMA's CFU/mL criteria: bacterial pathogen(s) found at baseline was/were reduced to <10^3 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Primary

End point timeframe:

TOC (Days 15-23)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	169		
Units: Participants	118	102		

Statistical analyses

Statistical analysis title	ME and Eradication

Statistical analysis description:

Treatment difference is the estimate of the difference in the overall success rate between the two treatment arms. The difference estimates and the 95% CIs are obtained based on Miettinen and Nurminen method.

Comparison groups	Meropenem/Vaborbactam v Piperacillin/Tazobactam
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Treatment Difference
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	16

Notes:

[3] - The noninferiority margin was a difference of 15%. Meropenem/vaborbactam was claimed to be non-inferior only if non-inferiority was demonstrated for microbial eradication at TOC in the ME Population.

Secondary: Proportion Of Participants In The m-MITT Population With Overall Success

End point title	Proportion Of Participants In The m-MITT Population With Overall Success

End point description:

This secondary outcome measure, evaluated only for the FDA, focused on the overall success in the m-MITT population at the EOIVT and TOC visits. Overall success at TOC was defined as a clinical outcome of Cured and a microbiologic outcome of Eradication. Overall success at EOIVT was defined as a clinical outcome of Cured or Improvement and a microbiologic outcome of Eradication. Cured was defined as the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP. Improvement was defined as lessening, incomplete resolution, or no worsening of the baseline signs and symptoms of cUTI or AP, but continued IV therapy was warranted. Eradication was defined using the FDA's CFU/mL criteria that the bacterial pathogen(s) found at baseline was/were reduced to <10^4 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Secondary

End point timeframe:

EOIVT (Days 5-14) and TOC (Days 15-23)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	182		
Units: Participants				
EOIVT	189	171		
TOC	143	128		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants In The ME Population With Overall Success

End point title	Proportion Of Participants In The ME Population With Overall Success

End point description:

This secondary outcome measure focused on the overall success in the ME population at the EOIVT and TOC visits. Overall success at TOC was defined as a clinical outcome of Cured and a microbiologic outcome of Eradication. Overall success at EOIVT was defined as a clinical outcome of Cured or Improvement and a microbiologic outcome of Eradication. Cured was defined as the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP. Improvement was defined as lessening, incomplete resolution, or no worsening of the baseline signs and symptoms of cUTI or AP, but continued IV therapy was warranted. Eradication was defined using the FDA's CFU/mL criteria that the bacterial pathogen(s) found at baseline was/were reduced to <10^4 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Secondary

End point timeframe:

EOIVT (Days 5-14) and TOC (Days 15-23)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	169		
Units: Participants				
EOIVT	178	165		
TOC	134	124		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants In The m-MITT Population Who Achieved A Microbiologic Outcome Of Eradication At The TOC Visit

End point title	Proportion Of Participants In The m-MITT Population Who Achieved A Microbiologic Outcome Of Eradication At The TOC Visit

End point description:

This secondary outcome measure focused on a microbiological outcome of Eradication in the m-MITT Population at 5 time points: Day 3, EOIVT, EOT, TOC, and LFU. Eradication was defined as a reduction in baseline bacterial pathogen(s) to <10^4 CFU/mL of urine culture (FDA) or <10^3 CFU/mL (EMA), and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	182		
Units: Participants				
Day 3: FDA	189	167		
EOIVT: FDA	188	168		
EOT: FDA	172	158		
TOC: FDA	132	113		
LFU: FDA	132	103		
Day 3: EMA	186	164		
EOIVT: EMA	188	168		
EOT: EMA	169	158		
TOC: EMA	128	105		
LFU: EMA	129	98		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants In The ME Population Who Achieved A Microbiologic Outcome Of Eradication

End point title	Proportion Of Participants In The ME Population Who Achieved A Microbiologic Outcome Of Eradication

End point description:

This secondary outcome measure focused on a microbiological outcome of Eradication the ME Population at 5 time points: Day 3, EOIVT, EOT, TOC, and LFU. Eradication was defined as a reduction in baseline bacterial pathogen(s) to <10^4 CFU/mL of urine culture (FDA) or <10^3 CFU/mL (EMA), and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	169		
Units: Participants				
Day 3: FDA	177	160		
EOIVT: FDA	178	166		
EOT: FDA	163	156		
TOC: FDA	122	109		
LFU: FDA	122	99		
Day 3: EMA	174	157		
EOIVT: EMA	178	166		
EOT: EMA	160	156		
TOC: EMA	118	102		
LFU: EMA	120	94		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants With A Clinical Outcome Of Cure In The m-MITT Population

End point title	Proportion Of Participants With A Clinical Outcome Of Cure In The m-MITT Population

End point description:

This secondary outcome measure focused on a clinical outcome of Cure in the m-MITT Population. A clinical outcome of Cure was defined as the following: at EOIVT, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP; at EOT, TOC, and LFU, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP such that no further antimicrobial therapy was warranted. Symptom resolution did not necessarily include baseline symptoms associated with anatomic abnormalities that predisposed to cUTI, such as symptoms associated with the presence of an indwelling urinary catheter. The clinical outcome of Cure was reported only at the EOIVT, EOT, TOC, and LFU visits, and improvement was reported only at Day 3, EOIVT, and EOT visits.

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	182		
Units: Participants				
Day 3: Improvement	186	171		
EOIVT: Cure	156	144		
EOIVT: Improvement	33	30		
EOT: Cure	179	167		
EOT: Improvement	4	3		
TOC: Cure	174	157		
LFU: Cure	166	143		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants With A Clinical Outcome Of Cure In The CE Population

End point title	Proportion Of Participants With A Clinical Outcome Of Cure In The CE Population

End point description:

This secondary outcome measure focused on a clinical outcome of Cure in the CE Population. A clinical outcome of Cure was defined as the following: at EOIVT, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP; at EOT, TOC, and LFU, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP such that no further antimicrobial therapy was warranted. Symptom resolution did not necessarily include baseline symptoms associated with anatomic abnormalities that predisposed to cUTI, such as symptoms associated with the presence of an indwelling urinary catheter. The clinical outcome of Cure was reported only at the EOIVT, EOT, TOC, and LFU visits, and improvement was reported only at the Day 3, EOIVT, and EOT visits.

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	258		
Units: Participants				
Day 3: Improvement	243	250		
EOIVT: Cure	202	206		
EOIVT: Improvement	45	46		
EOT: Cure	235	239		
EOT: Improvement	7	6		
TOC: Cure	231	224		
LFU: Cure	220	209		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion Of Participants With A Clinical Outcome Of Cure In The ME Population

End point title	Proportion Of Participants With A Clinical Outcome Of Cure In The ME Population

End point description:

This secondary outcome measure focused on a clinical outcome of Cure in the ME Population. A clinical outcome of Cure was defined as the following: at EOIVT, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP; at EOT, TOC, and LFU, the complete resolution or significant improvement of the baseline signs and symptoms of cUTI or AP such that no further antimicrobial therapy was warranted. Symptom resolution did not necessarily include baseline symptoms associated with anatomic abnormalities that predisposed to cUTI, such as symptoms associated with the presence of an indwelling urinary catheter. The clinical outcome of Cure was reported only at the EOIVT, EOT, TOC, and LFU visits, and improvement was reported only at the Day 3, EOIVT, and EOT visits.

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	169		
Units: Participants				
Day 3: Improvement	175	164		
EOIVT: Cure	148	138		
EOIVT: Improvement	30	30		
EOT: Cure	170	161		
EOT: Improvement	3	3		
TOC: Cure	164	153		
LFU: Cure	156	139		

Statistical analyses

No statistical analyses for this end point

Secondary: Per-Pathogen Microbiological Outcome (FDA) In The m-MITT Population

End point title	Per-Pathogen Microbiological Outcome (FDA) In The m-MITT Population

End point description:

This secondary outcome measure focused on the per-pathogen (E. cloacae, E. faecalis, E. coli, K. pneumoniae) microbiological outcome of Eradication in the m-MITT Population at 5 time points: Day 3, EOIVT, EOT, TOC, and LFU. Eradication was defined per the FDA criteria as a reduction in baseline bacterial pathogen(s) to <10^4 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178[4]	164[5]		
Units: Participant				
Day 3: E. cloacae	10	3		
EOIVT: E. cloacae	10	5		
EOT: E. cloacae	10	5		
TOC: E. cloacae	9	3		
LFU: E. cloacae	8	2		
Day 3: E. faecalis	13	14		
EOIVT: E. faecalis	13	14		
EOT: E. faecalis	13	14		
TOC: E. faecalis	7	12		
LFU: E. faecalis	11	10		
Day 3: E. coli	125	106		
EOIVT: E. coli	123	107		
EOT: E. coli	113	100		
TOC: E. coli	91	73		
LFU: E. coli	91	69		
Day 3: K. pneumoniae	29	26		
EOIVT: K. pneumoniae	29	26		
EOT: K. pneumoniae	27	24		
TOC: K. pneumoniae	19	15		
LFU: K. pneumoniae	15	13		

Notes:

[4] - E. cloacae (N=10); E. faecalis (N=13); E. coli (N=125); K. pneumoniae (N=30)

[5] - E. cloacae (N=5); E. faecalis (N=14); E. coli (N=117); K. pneumoniae (N=28)

Statistical analyses

No statistical analyses for this end point

Secondary: Per-Pathogen Microbiological Outcome (FDA) In The ME Population

End point title	Per-Pathogen Microbiological Outcome (FDA) In The ME Population

End point description:

This secondary outcome measure focused on the per-pathogen (E. cloacae, E. faecalis, E. coli, K. pneumoniae) microbiological outcome of Eradication in the ME Population at 5 time points: Day 3, EOIVT, EOT, TOC, and LFU. Eradication was defined per the FDA criteria as a reduction in baseline bacterial pathogen(s) to <10^4 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[6]	152[7]		
Units: Participants				
Day 3: E. cloacae	10	3		
EOIVT: E. cloacae	10	5		
EOT: E. cloacae	10	5		
TOC: E. cloacae	9	3		
LFU: E. cloacae	8	2		
Day 3: E. faecalis	11	14		
EOIVT: E. faecalis	11	14		
EOT: E. faecalis	11	13		
TOC: E. faecalis	6	12		
LFU: E. faecalis	9	10		
Day 3: E. coli	117	101		
EOIVT: E. coli	117	106		
EOT: E. coli	108	99		
TOC: E. coli	84	71		
LFU: E. coli	84	67		
Day 3: K. pneumoniae	28	25		
EOIVT: K. pneumoniae	28	26		
EOT: K. pneumoniae	26	24		
TOC: K. pneumoniae	18	14		
LFU: K. pneumoniae	15	12		

Notes:

[6] - E. cloacae (N=10); E. faecalis (N=11); E. coli (N=117); K. pneumoniae (N=28)

[7] - E. cloacae (N=5); E. faecalis (N=14); E. coli (N=106); K. pneumoniae (N=27)

Statistical analyses

No statistical analyses for this end point

Secondary: Per-Pathogen Microbiological Outcome (EMA) In The m-MITT Population

End point title	Per-Pathogen Microbiological Outcome (EMA) In The m-MITT Population

End point description:

This secondary outcome measure focused on the per-pathogen (E. cloacae, E. faecalis, E. coli, K. pneumoniae) microbiological outcome of Eradication in the m-MITT Population at 5 time points: Day 3, EOIVT, EOT, TOC, and LFU. Eradication was defined per the EMA criteria as a reduction in baseline bacterial pathogen(s) to <10^3 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178[8]	164[9]		
Units: Participants				
Day 3: E. cloacae	10	3		
EOIVT: E. cloacae	10	5		
EOT: E. cloacae	10	5		
TOC: E. cloacae	9	3		
LFU: E. cloacae	8	2		
Day 3: E. faecalis	13	14		
EOIVT: E. faecalis	13	14		
EOT: E. faecalis	12	13		
TOC: E. faecalis	5	11		
LFU: E. faecalis	9	9		
Day 3: E. coli	124	106		
EOIVT: E. coli	123	107		
EOT: E. coli	112	100		
TOC: E. coli	89	68		
LFU: E. coli	90	68		
Day 3: K. pneumoniae	29	24		
EOIVT: K. pneumoniae	29	26		
EOT: K. pneumoniae	27	24		
TOC: K. pneumoniae	19	14		
LFU: K. pneumoniae	15	12		

Notes:

[8] - E. cloacae (N=10); E. faecalis (N=13); E. coli (N=125); K. pneumoniae (N=30)

[9] - E. cloacae (N=5); E. faecalis (N=14); E. coli (N=117); K. pneumoniae (N=28)

Statistical analyses

No statistical analyses for this end point

Secondary: Per-Pathogen Microbiological Outcome (EMA) In The ME Population

End point title	Per-Pathogen Microbiological Outcome (EMA) In The ME Population

End point description:

This secondary outcome measure focused on the per-pathogen (E. cloacae, E. faecalis, E. coli, K. pneumoniae) microbiological outcome of Eradication in the ME Population at 5 time points: Day 3, EOIVT, EOT, TOC, and LFU. Eradication was defined per the EMA criteria as a reduction in baseline bacterial pathogen(s) to <10^3 CFU/mL of urine culture and a negative blood culture for an organism that was identified as an uropathogen (if repeated after positive at baseline blood culture).

End point type	Secondary

End point timeframe:

Day 3, EOIVT (Days 5-14), EOT (Days 10-14), TOC (Days 15-23), and LFU (Days 22-30)

End point values	Meropenem/Vaborbactam	Piperacillin/Tazobactam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[10]	152[11]		
Units: Participants				
Day 3: E. cloacae	10	3		
EOIVT: E. cloacae	10	5		
EOT: E. cloacae	10	5		
TOC: E. cloacae	9	3		
LFU: E. cloacae	8	2		
Day 3: E. faecalis	11	14		
EOIVT: E. faecalis	11	14		
EOT: E. faecalis	10	13		
TOC: E. faecalis	4	11		
LFU: E. faecalis	8	9		
Day 3: E. coli	117	101		
EOIVT: E. coli	117	106		
EOT: E. coli	107	99		
TOC: E. coli	82	67		
LFU: E. coli	83	66		
Day 3: K. pneumoniae	28	23		
EOIVT: K. pneumoniae	28	26		
EOT: K. pneumoniae	26	24		
TOC: K. pneumoniae	18	13		
LFU: K. pneumoniae	15	11		

Notes:

[10] - E. cloacae (N=10); E. faecalis (N=11); E. coli (N=117); K. pneumoniae (N=28)

[11] - E. cloacae (N=5); E. faecalis (N=14); E. coli (N=106); K. pneumoniae (N=27)

Statistical analyses

No statistical analyses for this end point

Secondary: PK Characterization Of Plasma Exposure Of Meropenem/Vaborbactam

End point title	PK Characterization Of Plasma Exposure Of Meropenem/Vaborbactam[12]

End point description:

This outcome measure focused on PK assessment of participants in the meropenem/vaborbactam group who met MITT criteria and had at least 1 plasma PK sample drawn. PK samples on Day 1 were taken 3-3.5 hours and 5-6 hours after the start of the first 3-hour IV study drug infusion. Samples were not collected around the 30-minute infusions. Samples were collected from both groups to maintain the blind; however, only PK samples for the meropenem/vaborbactam group were analyzed. The area under the concentration-time curve during 24 hours (AUC0-24) for Day 1 and at steady-state are presented in micrograms (ug)·hour/mL.

End point type	Secondary

End point timeframe:

Day 1

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Blood samples for analysis of plasma concentrations were collected from both groups to maintain the blind; however, only PK samples for the Meropenem/Vaborbactam Arm were analyzed.

End point values	Meropenem/Vaborbactam			
Subject group type	Reporting group			
Number of subjects analysed	272[13]			
Units: ug·hour/mL				
arithmetic mean (standard deviation)				
AUC0-24: Day 1	803 (± 45.3)			
AUC0-24: Steady-State	798 (± 60.6)			

Notes:

[13] - PK Population. AUC0-24 Steady-State estimates not available for 2 participants who received >3 doses

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (Screening) through Day 30 (Follow Up).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Meropenem/Vaborbactam

Reporting group description:

Meropenem/vaborbactam (meropenem 2 g plus vaborbactam 2 g), infused in 250 mL normal saline, administered IV over 3 hours, q8h, with 100 mL saline administered over 30 minutes q8h. Levofloxacin tablets administered orally as a 500-mg dose q24h after a minimum of 15 doses of IV meropenem/vaborbactam plus saline, if clinically indicated. Total treatment was 10 days, unless a participant had baseline bacteremia where up to 14 days of IV therapy could be administered.

Reporting group title	Piperacillin/Tazobactam

Reporting group description:

Piperacillin/tazobactam (piperacillin 4 g plus tazobactam 0.5 g), infused in 100 mL normal saline, administered IV over 30 minutes, q8h, with 250 mL saline administered over 30 minutes q8h. Levofloxacin tablets administered orally as a 500-mg dose q24h after a minimum of 15 doses of IV piperacillin/tazobactam plus saline, if clinically indicated. Total treatment was 10 days, unless a participant had baseline bacteremia where up to 14 days of IV therapy could be administered.

Serious adverse events	Meropenem/Vaborbactam	Piperacillin/Tazobactam	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 272 (4.04%)	12 / 273 (4.40%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 272 (0.37%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal neoplasm			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			

subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			

subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus uteric			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (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			
Salpingo-oophoritis			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 272 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 272 (0.37%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacterial sepsis			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 272 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 272 (0.00%)	2 / 273 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Meropenem/Vaborbactam	Piperacillin/Tazobactam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 272 (13.24%)	31 / 273 (11.36%)	
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 272 (8.82%)	12 / 273 (4.40%)	
occurrences (all)	24	12	
General disorders and administration site conditions			
Infusion site phlebitis			
subjects affected / exposed	6 / 272 (2.21%)	2 / 273 (0.73%)	
occurrences (all)	6	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 272 (3.31%)	12 / 273 (4.40%)	
occurrences (all)	9	12	
Infections and infestations			

Vaginal infection subjects affected / exposed occurrences (all)	1 / 272 (0.37%) 1	6 / 273 (2.20%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2014	The original protocol was dated 06 May 2014. The protocol was amended 3 times. Key changes in the first amendment included: • Added dose adjustment for renally impaired participants. • Permitted the use of trimethoprim/sulfamethoxazole, cefdinir, and cefpodoxime as step-down therapy for levofloxacin-resistant participants. • Included a Data Safety Monitoring Board. • Required an Acute Physiology and Chronic Health Evaluation (APACHE) II score <30 in participants who have a calculated APACHE II score. • Removed urinary incontinence, pyuria, and lower back pain from the list of signs and symptoms.
02 April 2015	The original protocol was dated 06 May 2014. The protocol was amended 3 times. Key changes in the second amendment included: • Modified weight criteria up to 185 kilograms. • Permitted the use of 1 dose of a short-acting antibiotic within 24 hours of randomization (up to 25% of participants). • Modified the proportion of participants with AP to at least 30%. • Excluded participants that could not tolerate the IV fluid volume of 1050 mL per day related to study drug infusions. • Excluded participants that have recent history of trauma to the pelvis or urinary tract. • Added collection of presence or history of Charlson Comorbidity Components to the participant's medical history. • Allowed for antibiotic coverage of any gram-positive organisms.
14 January 2016	The original protocol was dated 06 May 2014. The protocol was amended 3 times. The key change in the third amendment was: • Changing the sample size from 850 participants to 500 participants, with corresponding changes to the noninferiority margin from 10% to 15%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported