Clinical trial results:
A Phase 3, Randomized, Double-blind, Double-dummy, Multicenter, Prospective Study to Assess the Efficacy, Safety and Pharmacokinetics of Orally Administered Tebipenem Pivoxil Hydrobromide (SPR994) Compared to Intravenous Ertapenem in Patients with Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)

Summary

EudraCT number	2018-003671-35
Trial protocol	EE LV BG HU PL RO
Global end of trial date	27 May 2020

Results information

Result version number	v1 (current)
This version publication date	29 May 2022
First version publication date	29 May 2022

Trial information

Trial identification

Sponsor protocol code	SPR994-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03788967
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Spero Therapeutics, Inc.
Sponsor organisation address	Baarerstrasse 113, Zug, Switzerland, United States, 6300
Public contact	Angela Talley, Senior Vice President Clinical Development, +1 857-242-1575, atalley@sperotherapeutics.com
Scientific contact	Angela Talley, Senior Vice President Clinical Development, +1 857-242-1575, atalley@sperotherapeutics.com
Sponsor organisation name	Spero Therapeutics, Inc.
Sponsor organisation address	Baarerstrasse 113, Zug, Switzerland, United States, 6300
Public contact	Hanna Kwak, Spero Therapeutics, Inc., +1 857-242-1568, Hkwak@sperotherapeutics.com
Scientific contact	Hanna Kwak , Spero Therapeutics, Inc., +1 857-242-1568, Hkwak@sperotherapeutics.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	27 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to assess the overall response (combined clinical cure plus microbiological eradication) of oral Tebipenem Pivoxil Hydrobromide (TBPM-PI-HBr) compared to intravenous (IV) ertapenem in subjects ≥18 years of age with cUTI/AP and to assess the safety of oral TBPM-PI-HBr compared to IV ertapenem in subjects ≥18 years of age with cUTI/AP.

Protection of trial subjects:

All subjects signed the informed consent form provided by investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2019
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: 151
Country: Number of subjects enrolled	Czechia: 16
Country: Number of subjects enrolled	Estonia: 24
Country: Number of subjects enrolled	Georgia: 191
Country: Number of subjects enrolled	Hungary: 45
Country: Number of subjects enrolled	Latvia: 66
Country: Number of subjects enrolled	Moldova, Republic of: 24
Country: Number of subjects enrolled	Poland: 71
Country: Number of subjects enrolled	Romania: 104
Country: Number of subjects enrolled	Russian Federation: 196
Country: Number of subjects enrolled	Serbia: 166
Country: Number of subjects enrolled	Slovakia: 39
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Ukraine: 249
Country: Number of subjects enrolled	United States: 13

Worldwide total number of subjects	1372
EEA total number of subjects	516

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)	774
From 65 to 84 years	556
85 years and over	42

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 95 study centers in Bulgaria, Czech Republic, Estonia, Georgia, Hungary, Latvia, Moldova, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Ukraine, and the United States from 03 June 2019 to 27 May 2020.

Pre-assignment

Screening details:

Subjects with diagnosis of complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP) were enrolled to receive TBPM-PI-HBr and Ertapenem.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	TBPM-PI-HBr 600 mg

Arm description:

TBPM-PI-HBr 600 mg (300 mg × 2) film-coated tablets, administered orally three times per day (every 8 hours [q8h] ± 0.5 h) plus a single dummy IV infusion over 30 minutes (min) once daily (every 24 hours [q24h] ± 0.5 h) up to Day 15; participants with moderate renal insufficiency (creatinine clearance [CrCl] >30 to ≤50 mL/min) required TBPM-PI-HBr dosage adjustment to 300 mg (one tablet) q8h ± 0.5 h.

Arm type	Experimental
Investigational medicinal product name	Tebipenem Pivoxil Hydrobromide (TBPM-PI-HBr)
Investigational medicinal product code	
Other name	SPR994
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TBPM-PI-HBr 600 mg (300 mg × 2) film-coated tablet administered orally every 8 hours (q8h), per day for up to Day 14.

Arm title	Ertapenem 1g

Arm description:

Ertapenem for IV injection, administered as a 1-gram IV infusion over 30 min once daily (q24h ± 0.5 h) plus dummy placebo tablets administered orally q8h (±0.5 h) up to Day 14; no dose adjustment of ertapenem was required for participants with renal insufficiency.

Arm type	Experimental
Investigational medicinal product name	Ertapenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Ertapenem 1 g IV infusion administered over 30 min once daily (QD) for up to Day 14.

Number of subjects in period 1	TBPM-PI-HBr 600 mg	Ertapenem 1g
Started	685	687
Micro-Intent-to-Treat (ITT) Population	449 [1]	419 [2]
Completed	653	663
Not completed	32	24
Subject Non-Compliance/Uncooperativeness	3	6
Adverse event, non-fatal	1	1
COVID-19	1	2
Lost to follow-up	14	10
Subject Withdrawal of Consent	13	5

Notes:

[1] - 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: Micro-ITT=all randomized participants with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens.

[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: Micro-ITT=all randomized participants with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens.

Baseline characteristics

Reporting groups	
Reporting group title	TBPM-PI-HBr 600 mg

Reporting group description:

TBPM-PI-HBr 600 mg (300 mg × 2) film-coated tablets, administered orally three times per day (every 8 hours [q8h] ± 0.5 h) plus a single dummy IV infusion over 30 minutes (min) once daily (every 24 hours [q24h] ± 0.5 h) up to Day 15; participants with moderate renal insufficiency (creatinine clearance [CrCl] >30 to ≤50 mL/min) required TBPM-PI-HBr dosage adjustment to 300 mg (one tablet) q8h ± 0.5 h.

Reporting group title	Ertapenem 1g

Reporting group description:

Ertapenem for IV injection, administered as a 1-gram IV infusion over 30 min once daily (q24h ± 0.5 h) plus dummy placebo tablets administered orally q8h (±0.5 h) up to Day 14; no dose adjustment of ertapenem was required for participants with renal insufficiency.

Reporting group values	TBPM-PI-HBr 600 mg	Ertapenem 1g	Total
Number of subjects	685	687	1372
Age categorical Units: Subjects			
Adults (18-64 years)	387	387	774
From 65-84 years	275	281	556
85 years and over	23	19	42
Age continuous Units: years			
arithmetic mean	56.7	57.2	
standard deviation	± 18.68	± 18.23	-
Gender categorical Units: Subjects			
Female	368	389	757
Male	317	298	615
Ethnicity Units: Subjects			
Hispanic or Latino	13	5	18
Not Hispanic or Latino	672	682	1354
Race Units: Subjects			
Asian	3	4	7
Black or African American	6	6	12
White	676	677	1353

End points

End points reporting groups

Reporting group title	TBPM-PI-HBr 600 mg

Reporting group description:

TBPM-PI-HBr 600 mg (300 mg × 2) film-coated tablets, administered orally three times per day (every 8 hours [q8h] ± 0.5 h) plus a single dummy IV infusion over 30 minutes (min) once daily (every 24 hours [q24h] ± 0.5 h) up to Day 15; participants with moderate renal insufficiency (creatinine clearance [CrCl] >30 to ≤50 mL/min) required TBPM-PI-HBr dosage adjustment to 300 mg (one tablet) q8h ± 0.5 h.

Reporting group title	Ertapenem 1g

Reporting group description:

Ertapenem for IV injection, administered as a 1-gram IV infusion over 30 min once daily (q24h ± 0.5 h) plus dummy placebo tablets administered orally q8h (±0.5 h) up to Day 14; no dose adjustment of ertapenem was required for participants with renal insufficiency.

Primary: Overall Response (Combined Clinical Cure and Microbiological Eradication) at Test-of-Cure (TOC) in Micro Intent-to-Treat Population

End point title	Overall Response (Combined Clinical Cure and Microbiological Eradication) at Test-of-Cure (TOC) in Micro Intent-to-Treat Population

End point description:

Overall response is participants with combined clinical cure and microbiological eradication. Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Microbiological eradication is defined as reduction of Baseline urine pathogen(s) to <10^3 colony forming unit/milliliter (CFU/mL) and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. Microbiological intent-to-treat population (Micro-ITT) included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens.

End point type	Primary

End point timeframe:

Day 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: subjects	264	258		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g

Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Risk Difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	3.2

Notes:

[1] - The non-inferiority hypothesis test was a 1-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the 95% CI for the difference in overall response was greater than -12.5%, non-inferiority was declared.

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) in The Safety Population

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) in The Safety Population[2]

End point description:

An Adverse Event (AE) was defined as any untoward medical occurrence in a subject or clinical investigation participant administered a pharmaceutical product, which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product. Safety analysis population included all randomized subjects who received any amount of study drug.

End point type	Primary

End point timeframe:

From the first dose of administration up to Day 25 post-treatment ± 2 days (up to approximately 27 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified for this end point.

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	685	687		
Units: subjects	176	176		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response (Combined Clinical Cure Plus Microbiological Eradication) At Test-Of-Cure (TOC) In The Microbiologically Evaluable (ME) - TOC Population

End point title	Overall Response (Combined Clinical Cure Plus Microbiological Eradication) At Test-Of-Cure (TOC) In The Microbiologically Evaluable (ME) - TOC Population

End point description:

Overall response is number of subjects with combined clinical cure and microbiological eradication. Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of cUTI

or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Microbiological eradication is defined as reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. Microbiologically evaluable (ME) - TOC population included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the evaluability review plan (ERP).

End point type	Secondary

End point timeframe:

Day 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	376		
Units: subjects	254	247		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ertapenem 1g v TBPM-PI-HBr 600 mg
Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	1.9

Secondary: Clinical Cure at End-of-Treatment (EOT), TOC, and Sustained Clinical Cure at Late Follow-Up (LFU) in the Micro-ITT Population

End point title	Clinical Cure at End-of-Treatment (EOT), TOC, and Sustained Clinical Cure at Late Follow-Up (LFU) in the Micro-ITT Population

End point description:

Clinical cure is defined as number of subjects with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Sustained clinical cure is defined as subjects who wet criteria for clinical cure at TOC and remained free of signs and symptoms of cUTI or AP at LFU. Micro-ITT included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens.

End point type	Secondary

End point timeframe:

Days 15 (EOT), Day 19 (TOC) and Day 25 (LFU)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: subjects				
End-of-Treatment (EOT)	446	410		
Test-of-Cure (TOC)	418	392		
Late Follow-Up (LFU)	398	377		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 (EOT)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	3.4

Statistical analysis title	Statistical Analysis 3 (LFU)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	2.6

Statistical analysis title	Statistical Analysis 2 (TOC)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g

Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	2.8

Secondary: Clinical Cure at EOT in the Clinically Evaluable (CE-EOT) Population

End point title	Clinical Cure at EOT in the Clinically Evaluable (CE-EOT) Population

End point description:

Clinical cure is defined as number of subjects with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted. CE-EOT population is a subset which included subjects who meet the definition for the ITT population, have no important protocol deviations that would affect the assessment of efficacy, and had an outcome assessed as clinical cure or clinical failure at EOT.

End point type	Secondary

End point timeframe:

Day 15 (EOT)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	677	674		
Units: subject	673	665		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	1351
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2

Secondary: Clinical Cure at TOC in the CE-TOC Populations

End point title	Clinical Cure at TOC in the CE-TOC Populations

End point description:

Clinical cure is defined as number of subjects with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted. CE-TOC population is a subset which included participants who meet the definition for the ITT population, have no important protocol deviations that would affect the assessment of efficacy, and had an outcome assessed as clinical cure or clinical failure at TOC.

End point type	Secondary

End point timeframe:

Day 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	641	637		
Units: subjects	611	617		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	1278
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	0.6

Secondary: Sustained Clinical Cure at LFU in the CE-LFU Population

End point title	Sustained Clinical Cure at LFU in the CE-LFU Population

End point description:

Clinical cure is defined as number of subjects with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Sustained clinical cure is defined as participants who met criteria for clinical cure at TOC and remained free of signs and symptoms of cUTI or AP at LFU. CE-LFU population is a subset which included subjects who meet the definition for the ITT population, have no important protocol deviations that would affect the assessment of efficacy, and had an outcome assessed as clinical cure or clinical failure at LFU.

End point type	Secondary
End point timeframe:	
Day 25 (LFU)	

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	596	596		
Units: subjects	556	559		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	1192
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	2.3

Secondary: Clinical Cure at EOT in the ME-EOT Population

End point title	Clinical Cure at EOT in the ME-EOT Population
End point description:	
Clinical cure is defined as number of participants with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted. ME-EOT population is a subset which included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP.	
End point type	Secondary
End point timeframe:	
Day 15 (EOT)	

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	401		
Units: subjects	437	394		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	840
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	3.2

Secondary: Clinical Cure at TOC in the ME-TOC Population

End point title	Clinical Cure at TOC in the ME-TOC Population

End point description:

Clinical cure is defined as number of participants with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted. ME-TOC population is a subset which included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP.

End point type	Secondary

End point timeframe:

Day 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	376		
Units: subjects	390	363		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g

Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	0.8

Secondary: Sustained Clinical Cure at LFU in the ME-LFU Population

End point title	Sustained Clinical Cure at LFU in the ME-LFU Population

End point description:

Clinical cure is defined as number of participants with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Sustained clinical cure is defined as participants who met criteria for clinical cure at TOC and remained free of signs and symptoms of cUTI or AP at LFU. ME-LFU population is a subset which included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP.

End point type	Secondary

End point timeframe:

Day 25 (LFU)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	391	353		
Units: subjects	360	329		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	744
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	2.6

Secondary: By-Patient Microbiological Eradication at EOT, TOC, Sustained Microbiological Eradication at LFU in the Micro-ITT Population

End point title	By-Patient Microbiological Eradication at EOT, TOC, Sustained Microbiological Eradication at LFU in the Micro-ITT Population

End point description:

Microbiological eradication is defined as reduction of baseline urine pathogen(s) to <10^3 colony forming unit/milliliter (CFU/mL) and negative repeated blood culture if blood culture was positive for uropathogen growth at baseline. Sustained Microbiological Eradication is defined subjects with microbiologic eradication at the TOC and no subsequent urine culture after TOC demonstrating recurrence of the original baseline uropathogen at ≥10^5 CFU/mL. Micro-ITT include all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens.

End point type	Secondary

End point timeframe:

Days 15 (EOT), 19 (TOC) and 25 (LFU)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: subjects				
EOT	439	403		
TOC	267	266		
LFU	257	244		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 (EOT)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	4.1

Statistical analysis title	Copy of Statistical Analysis 3 (LFU)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g

Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	5

Statistical analysis title	Statistical Analysis 2 (TOC)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	1.9

Secondary: By-Pathogen Microbiological Eradication Rate at EOT in the Micro-ITT Populations

End point title	By-Pathogen Microbiological Eradication Rate at EOT in the Micro-ITT Populations

End point description:

Microbiological eradication rate is percentage of participants with microbiological eradication. Microbiological eradication is defined as reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at baseline. Micro-ITT included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one/more uropathogens. Microbiological eradication rate is percentage of pathogens being eradicated from overall number of pathogens analyzed. 'n' = Number analyzed is number of pathogens analyzed at the given timepoint.

End point type	Secondary

End point timeframe:

Day 15 (EOT)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: percentage of pathogens eradicated				
number (not applicable)				
Enterobacterales, Citrobacter braakii (n=0, 2)	0.0	100		
Enterobacterales, Citrobacter freundii (n=4, 3)	75.0	66.7		
Enterobacterales, Citrobacter koseri (n=3, 4)	100	100		
Enterobacterales, Enterobacter amnigenus (n=0, 1)	0.0	100		
Enterobacterales, Enterobacter asburiae (n=0, 1)	0.0	100		
Enterobacterales, Enterobacter bugandensis (n=0, 1	0.0	100		
Enterobacterales, Enterobacter cloacae (n=11, 8)	90.9	100		
Enterobacterales, Escherichia coli (n=287, 270)	98.3	96.7		
Enterobacterales, Klebsiella aerogenes (n=1, 1)	100	0.0		
Enterobacterales, Klebsiella oxytoca (n=4, 3)	100	100		
Enterobacterales, Klebsiella pneumoniae (n=53, 71)	98.1	98.6		
Enterobacterales, Klebsiella variicola (n=2, 4)	100	100		
Enterobacterales, Morganella morganii (n=2, 4)	100	100		
Enterobacterales, Proteus hauseri (n=2, 0)	100	0.0		
Enterobacterales, Proteus mirabilis (n=35, 23)	97.1	100		
Enterobacterales, Proteus penneri (n=0, 1)	0.0	100		
Enterobacterales, Proteus vulgaris (n=0, 1)	0.0	100		
Enterobacterales, Providencia rettgeri (n=4, 3)	100	100		
Enterobacterales, Providencia stuartii (n=1, 1)	100	100		
Enterobacterales,Raoultella ornithinolytica(n=2,0)	100	0.0		
Enterobacterales, Serratia liquefaciens (n=0, 1)	0.0	100		
Enterobacterales, Serratia marcescens (n=4, 2)	100	100		
Gram Positive, Enterococcus faecalis (n=58, 36)	94.8	91.7		
Gram Positive, Enterococcus faecium (n=5, 2)	100	100		
Gram Positive, Enterococcus hirae (n=1, 0)	100	0.0		
Gram Positive, Staphylococcus aureus (n=5, 8)	100	75.0		
Gram Positive, Staphylococcus lugdunensis (n=2, 1)	100	100		

Gram Positive,Staphylococcus saprophyticus(n=4,6)	100	100		
Gram Positive, Streptococcus gallolyticus (n=1, 0)	100	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: By-Pathogen Microbiological Eradication Rate at TOC in the Micro-ITT Populations

End point title	By-Pathogen Microbiological Eradication Rate at TOC in the Micro-ITT Populations

End point description:

Microbiological eradication rate is percentage of participants with microbiological eradication. Microbiological eradication is defined as reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at baseline. Micro-ITT included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one/more uropathogens. Microbiological eradication rate is percentage of pathogens being eradicated from overall number of subjects analyzed. 'n' = Number analyzed is number of pathogens analyzed at the given timepoint.

End point type	Secondary

End point timeframe:

Days 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: percentage of pathogen eradication				
number (not applicable)				
Enterobacterales, Citrobacter braakii (n=0, 2)	0.0	100		
Enterobacterales, Citrobacter freundii (n=4, 3)	50.0	100		
Enterobacterales, Citrobacter koseri (n=3, 4)	66.7	50.0		
Enterobacterales, Enterobacter amnigenus (n=0, 1)	0.0	100		
Enterobacterales, Enterobacter asburiae (n=0, 1)	0.0	100		
Enterobacterales, Enterobacter bugandensis(n=0, 1)	0.0	100		
Enterobacterales, Enterobacter cloacae (n=11, 8)	54.5	50.0		
Enterobacterales, Escherichia coli (n=287, 270)	62.7	65.2		
Enterobacterales, Klebsiella aerogenes (n=1, 1)	0.0	0.0		
Enterobacterales, Klebsiella oxytoca (n=4, 3)	75.0	33.3		

Enterobacterales, Klebsiella pneumoniae (n=53, 71)	45.3	63.4		
Enterobacterales, Klebsiella variicola (n=2, 4)	50.0	75.0		
Enterobacterales, Morganella morganii (n=4, 1)	100	100		
Enterobacterales, Proteus hauseri (n=2, 0)	100	0.0		
Enterobacterales, Proteus mirabilis (n=35, 23)	48.6	69.6		
Enterobacterales, Proteus penneri (n=0, 1)	0.0	100		
Enterobacterales, Proteus vulgaris (n=0, 1)	0.0	100		
Enterobacterales, Providencia rettgeri (n=4, 3)	100	100		
Enterobacterales, Providencia stuartii (n=1, 1)	0.0	100		
Enterobacterales,Raoultella ornithinolytica(n=2,0)	100	0.0		
Enterobacterales, Serratia liquefaciens (n=0, 1)	0.0	100		
Enterobacterales, Serratia marcescens (n=4, 2)	50.0	100		
Gram Positive, Enterococcus faecalis (n=58,36)	67.2	55.6		
Gram Positive, Enterococcus faecium (n=5, 2)	100	100		
Gram Positive, Enterococcus hirae (n=1, 0)	100	0.0		
Gram Positive, Staphylococcus aureus (n=5, 8)	100	37.5		
Gram Positive, Staphylococcus lugdunensis (n=2, 1)	100	100		
Gram Positive, Staphylococcus saprophyticus(n=4,6)	100	83.3		
Gram Positive, Streptococcus gallolyticus (n=1, 0)	100	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: By-Pathogen Sustained Microbiological Eradication Rate at LFU in the Micro-ITT Populations

End point title	By-Pathogen Sustained Microbiological Eradication Rate at LFU in the Micro-ITT Populations

End point description:

Microbiological eradication rate is percentage of participants with microbiological eradication. Microbiological eradication is defined as reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at baseline. Sustained Microbiological Eradication is defined participants with microbiologic eradication at the TOC and no subsequent urine culture after TOC demonstrating recurrence of the original baseline uropathogen at ≥10^5 CFU/mL. Micro-ITT included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens. 'n' = Number analyzed is number of pathogens analyzed at the given timepoint.

End point type	Secondary

End point timeframe:
Days 25 (LFU)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: percentage of pathogen eradication				
number (not applicable)				
Enterobacterales (pathogens n=449, 419)	57.6	60.9		
Citrobacter braakii (pathogens n=0, 2)	0.0	100		
Citrobacter freundii (pathogens n=4, 3)	50.0	100		
Citrobacter koseri (pathogens n=3, 4)	66.7	50.0		
Enterobacter amnigenus (pathogens n=0, 1)	0.0	100		
Enterobacter asburiae (pathogens n=0, 1)	0.0	0.0		
Enterobacter bugandensis (pathogens n=0, 1)	0.0	100		
Enterobacter cloacae (pathogens n=11, 8)	54.5	37.5		
Enterococcus faecalis (pathogens n=58, 36)	63.8	50.0		
Enterococcus faecium (pathogens n=5, 2)	100	100		
Enterococcus hirae (pathogens n=1, 0)	100	0.0		
Escherichia coli (pathogens n=287, 270)	59.9	60.0		
Klebsiella aerogenes (pathogens n=1, 1)	0.0	0.0		
Klebsiella oxytoca (pathogens n=4, 3)	75.0	33.3		
Klebsiella pneumoniae (pathogens n=53, 71)	43.4	60.6		
Klebsiella variicola (pathogens n=2, 4)	50.0	75.0		
Morganella morganii (pathogens n=4, 1)	100	100		
Proteus hauseri (pathogens n=2,0)	100	0.0		
Proteus mirabilis (pathogens n=35, 23)	48.6	60.9		
Proteus penneri (pathogens n=0, 1)	0.0	100		
Proteus vulgaris (pathogens n=0, 1)	0.0	100		
Providencia rettgeri (pathogens n=4,3)	100	100		
Providencia stuartii (pathogens n=1, 1)	0.0	100		
Raoultella ornithinolytica (pathogens n=2,0)	100	0.0		
Serratia liquefaciens (pathogens n=0, 1)	0.0	100		
Serratia marcescens (pathogens n=4,2)	50.0	100		
Staphylococcus aureus (pathogens n=5,8)	100	37.5		
Staphylococcus lugdunensis (pathogens n=2,1)	100	100		
Staphylococcus saprophyticus (pathogens n=4,6)	100	83.3		
Staphylococcus gallolyticus (pathogens n=1,0)	100	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: By-Patient Microbiological Eradication at EOT in the ME-EOT Population

End point title	By-Patient Microbiological Eradication at EOT in the ME-EOT Population

End point description:

Microbiological eradication is defined as number of participants with reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. ME-EOT population is a subset which included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP.

End point type	Secondary

End point timeframe:

Day 15 (EOT)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	401		
Units: subjects	436	399		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	840
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.2

Secondary: By-Patient Microbiological Eradication at TOC in the ME-TOC Population

End point title	By-Patient Microbiological Eradication at TOC in the ME-TOC Population

End point description:

Microbiological eradication is defined as number of participants with reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. ME-TOC population is a subset which included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP.

End point type	Secondary

End point timeframe:

Day 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	376		
Units: subjects	257	254		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	0.7

Secondary: By-Patient Sustained Microbiological Eradication at LFU in the ME-LFU Population

End point title	By-Patient Sustained Microbiological Eradication at LFU in the ME-LFU Population

End point description:

Microbiological eradication is defined as number of participants with reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. Sustained Microbiological Eradication is defined participants with microbiologic eradication at the TOC and no subsequent urine culture after TOC demonstrating recurrence of the original baseline uropathogen at ≥10^5 CFU/mL. Sustained Microbiological Eradication is defined participants with microbiologic eradication at the TOC and no subsequent urine culture after TOC demonstrating recurrence of the original baseline uropathogen at ≥10^5 CFU/mL. ME-LFU population included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP. Number analyzed is number of pathogens analyzed at the given timepoint.

End point type	Secondary

End point timeframe:

Day 25 (LFU)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	391	353		
Units: subjects	234	216		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ertapenem 1g v TBPM-PI-HBr 600 mg
Number of subjects included in analysis	744
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	5.3

Secondary: By-pathogen Microbiological Eradication Rate at EOT in the ME-EOT Population

End point title	By-pathogen Microbiological Eradication Rate at EOT in the ME-EOT Population

End point description:

Microbiological eradication is defined as percentage of participants with reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. ME-EOT population is a subset which included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP. Microbiological eradication rate is the percentage of pathogens being eradicated from the overall number of pathogens analyzed. Overall number of subjects analysed are the subjects with data available for analysis. 'n' = Number analyzed is number of pathogens analyzed at the given timepoint.

End point type	Secondary

End point timeframe:

Day 15 (EOT)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	401		
Units: percentage of pathogen eradication				
number (not applicable)				
Enterobacterales, Citrobacter braakii (n=0, 2)	0.0	100		
Enterobacterales, Citrobacter freundii (n=3, 2)	100	100		
Enterobacterales, Citrobacter koseri (n=3, 4)	100	100		
Enterobacterales, Enterobacter amnigenus (n=0, 1)	0.0	100		
Enterobacterales, Enterobacter asburiae (n=0, 1)	0.0	100		
Enterobacterales, Enterobacter bugandensis(n=0, 1)	0.0	100		
Enterobacterales, Enterobacter cloacae (n=11, 8)	90.9	100		
Enterobacterales, Escherichia coli (n=282, 257)	99.6	100		
Enterobacterales, Klebsiella aerogenes (n=1, 0)	100	0.0		
Enterobacterales, Klebsiella oxytoca (n=4, 3)	100	100		
Enterobacterales, Klebsiella pneumoniae (n=52, 70)	100	100		
Enterobacterales, Klebsiella variicola (n=2, 4)	100	100		
Enterobacterales, Morganella morganii (n=4, 1)	100	100		
Enterobacterales, Proteus hauseri (n=2, 0)	100	0.0		
Enterobacterales, Proteus mirabilis (n=34, 23)	100	100		
Enterobacterales, Proteus penneri (n=0, 1)	0.0	100		
Enterobacterales, Proteus vulgaris (n=0, 1)	0.0	100		
Enterobacterales, Providencia rettgeri (n=4, 3)	100	100		
Enterobacterales, Providencia stuartii (n=1, 1)	100	100		
Enterobacterales,Raoultella ornithinolytica(n=2,0)	100	0.0		
Enterobacterales, Serratia liquefaciens (n=0, 1)	0.0	100		
Enterobacterales, Serratia marcescens (n=4, 2)	100	100		
Gram Positive, Enterococcus faecalis (n=54, 34)	98.1	97.1		
Gram Positive, Enterococcus faecium (n=5, 2)	100	100		
Gram Positive, Enterococcus hirae (n=1, 0)	100	0.0		
Gram Positive, Staphylococcus aureus (n=5, 7)	100	85.7		
Gram Positive, Staphylococcus lugdunensis (n=2, 1)	100	100		

Gram Positive,Staphylococcus saprophyticus(n=4,6)	100	100		
Gram Positive, Streptococcus gallolyticus (n=1, 0)	100	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: By-pathogen Microbiological Eradication Rate at TOC in the ME-TOC Populations

End point title	By-pathogen Microbiological Eradication Rate at TOC in the ME-TOC Populations

End point description:

Microbiological eradication is defined as reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. ME-TOC population is a subset which included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP. Microbiological eradication rate is the percentage of pathogens being eradicated from the overall number of pathogens analyzed. 'n' = Number analyzed is number of pathogens analyzed at the given timepoint.

End point type	Secondary

End point timeframe:

Day 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	376		
Units: percentage of pathogen eradication				
number (not applicable)				
Enterobacterales, Citrobacter braakii (n=0, 2)	0.0	100		
Enterobacterales, Citrobacter freundii (n=3, 2)	66.7	100		
Enterobacterales, Citrobacter koseri (n=3, 3)	66.7	66.7		
Enterobacterales, Enterobacter amnigenus (n=0, 1)	0.0	100		
Enterobacterales, Enterobacter asburiae (n=0, 1)	0.0	100		
Enterobacterales, Enterobacter bugandensis (n=0, 1	0.0	100		
Enterobacterales, Enterobacter cloacae (n=11, 8)	54.5	50.0		
Enterobacterales, Escherichia coli (n=263, 243)	65.8	68.3		
Enterobacterales, Klebsiella aerogenes (n=1, 0)	0.0	0.0		
Enterobacterales, Klebsiella oxytoca (n=3, 2)	100	50.0		

Enterobacterales, Klebsiella pneumoniae (n=49, 62)	49.0	71.0		
Enterobacterales, Klebsiella variicola (n=2, 4)	50.0	75.0		
Enterobacterales, Morganella morganii (n=4, 1)	100	100		
Enterobacterales, Proteus hauseri (n=2, 0)	100	0.0		
Enterobacterales, Proteus mirabilis (n=31, 21)	51.6	76.2		
Enterobacterales, Proteus penneri (n=0, 1)	0.0	100		
Enterobacterales, Proteus vulgaris (n=0, 1)	0.0	100		
Enterobacterales, Providencia rettgeri (n=3, 2)	100	100		
Enterobacterales, Providencia stuartii (n=1, 1)	0.0	100		
Enterobacterales,Raoultella ornithinolytica(n=2,0)	100	0.0		
Enterobacterales, Serratia liquefaciens (n=0, 1)	0.0	100		
Enterobacterales, Serratia marcescens (n=3, 2)	66.7	100		
Gram Positive, Enterococcus faecalis (n=53, 33)	69.8	57.6		
Gram Positive, Enterococcus faecium (n=5, 2)	100	100		
Gram Positive, Enterococcus hirae (n=1, 0)	100	0.0		
Gram Positive, Staphylococcus aureus (n=4, 6)	100	50.0		
Gram Positive, Staphylococcus lugdunensis (n=2, 1)	100	100		
Gram Positive,Staphylococcus saprophyticus(n=4,6)	100	83.3		
Gram Positive, Streptococcus gallolyticus (n=1, 0)	100	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: By-pathogen Sustained Microbiological Eradication at LFU in the ME-LFU Populations

End point title	By-pathogen Sustained Microbiological Eradication at LFU in the ME-LFU Populations

End point description:

Microbiological eradication is defined as percentage of participants with reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. Sustained Microbiological Eradication is defined participants with microbiologic eradication at the TOC and no subsequent urine culture after TOC demonstrating recurrence of the original baseline uropathogen at ≥10^5 CFU/mL. ME population included subjects who met the definitions of both the micro-ITT Population and CE Population and were defined for each visit for the analyses in the ME Population at each respective visit as outlined in the ERP. Microbiological eradication rate is the percentage of pathogens being eradicated from the overall number of pathogens analyzed. 'n' = Number analyzed is number of pathogens analyzed at the given timepoint.

End point type	Secondary

End point timeframe:
Day 25 (LFU)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	391	353		
Units: percentage of pathogen eradication				
number (not applicable)				
Enterobacterales (pathogens n=391, 353)	60.6	64.7		
Citrobacter braakii (pathogens n=0, 2)	0	100		
Citrobacter freundii (pathogens n=3, 3)	66.7	100		
Citrobacter koseri (pathogens n=2, 3)	100	66.7		
Enterobacter amnigenus (pathogens n=0, 1)	0	100		
Enterobacter asburiae (pathogens n=0, 1)	0	0		
Enterobacter bugandensis (pathogens n=0, 1)	0	100		
Enterobacter cloacae (pathogens n=9, 6)	55.6	33.3		
Enterococcus faecalis (pathogens n=51, 34)	66.7	52.9		
Enterococcus faecium (pathogens n=5, 2)	100	100		
Enterococcus hirae (pathogens n=1, 0)	100	0.0		
Escherichia coli (pathogens n=250, 228)	62.4	61.8		
Klebsiella aerogenes (pathogens n=1, 0)	0.0	0.0		
Klebsiella oxytoca (pathogens n=2, 2)	100	50.0		
Klebsiella pneumoniae (pathogens n=45, 57)	46.7	68.4		
Klebsiella variicola (pathogens n=2, 3)	50.0	66.7		
Morganella morganii (pathogens n=4, 1)	100	100		
Proteus hauseri (pathogens n=2,0)	100	0.0		
Proteus mirabilis (pathogens n=29, 40)	51.7	70.0		
Proteus penneri (pathogens n=0, 1)	0.0	100		
Proteus vulgaris (pathogens n=0, 1)	0.0	100		
Providencia rettgeri (pathogens n=3, 3)	100	100		
Providencia stuartii (pathogens n=1, 1)	0.0	100		
Raoultella ornithinolytica (pathogens n=2, 0)	100	0.0		
Serratia liquefaciens (pathogens n=0, 1)	0.0	100		
Serratia marcescens (pathogens n=3, 2)	66.7	100		
Staphylococcus aureus (pathogens n=4, 6)	100	50.0		
Staphylococcus lugdunensis (pathogens n=2, 1)	100	100		
Staphylococcus saprophyticus (pathogens n=4, 5)	100	80.0		
Staphylococcus gallolyticus (pathogens n=1, 0)	100	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (Combined Clinical Cure Plus Microbiological Eradication) at TOC In Subgroup Including: Stratified Infection Category

End point title	Overall Response Rate (Combined Clinical Cure Plus Microbiological Eradication) at TOC In Subgroup Including: Stratified Infection Category

End point description:

Overall response rate is percentage of participants with combined clinical cure plus microbiological eradication. Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Microbiological eradication is defined as reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. Micro-ITT population included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥105 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens. n=number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Day 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: percentage of subjects				
number (not applicable)				
AP (n=226, 201)	65.9	70.6		
cUTI (n=223, 218)	51.6	53.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 (AP)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-4.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	4.1

Statistical analysis title	Statistical Analysis 2 (cUTI)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	7.7

Secondary: Overall Response Rate (Combined Clinical Cure Plus Microbiological Eradication) at TOC In Subgroup Stratified Age Category

End point title	Overall Response Rate (Combined Clinical Cure Plus Microbiological Eradication) at TOC In Subgroup Stratified Age Category

End point description:

Overall response rate is percentage of participants with combined clinical cure plus microbiological eradication. Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Microbiological eradication is defined as reduction of baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at baseline. Micro-ITT population included all randomized participants with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥105 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens. 'n' indicated number analysed is number of participants with data available for analysis at specific timepoint.

End point type	Secondary

End point timeframe:

Day 19 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: percentage of subjects				
number (not applicable)				
≥18 to <65 years (n=246, 222)	66.7	65.3		
≥65 to <75 years (n=122, 132)	49.2	57.6		

≥75 years (n=81, 65)	49.4	56.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 (≥18 to <65 years)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	9.9

Statistical analysis title	Statistical Analysis 2 (≥65 to <75 years)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-8.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.6
upper limit	3.8

Statistical analysis title	Statistical Analysis 3 (≥75 years)
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.8
upper limit	8.7

Secondary: Overall Response Rate (Combined Clinical Cure Plus Microbiological Eradication) at TOC In Subgroup Including Region

End point title	Overall Response Rate (Combined Clinical Cure Plus Microbiological Eradication) at TOC In Subgroup Including Region

End point description:

Overall response rate is percentage of participants with combined clinical cure plus microbiological eradication. Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Microbiological eradication is defined as reduction of Baseline urine pathogen(s) to <10^3 CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline. Micro-ITT included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens. Number analyzed is number of subjects with data available for analysis at specific timepoint. 'The point estimate and confidence interval (CI) presented is for Central and eastern Europe subgroup'

End point type	Secondary

End point timeframe:

Day 25 (TOC)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: percentage of subjects				
number (not applicable)				
Central and Eastern Europe (n=443, 413)	58.9	62.0		
South Africa (n=3, 2)	100	0.0		
United States (n=3, 4)	0.0	50.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1- Central and Eastern Europe
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk Difference
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	3.5

Secondary: Time (Days) to Resolution or Improvement of Signs and Symptoms of cUTI and AP Present a Baseline in the Micro-ITT Populations

End point title	Time (Days) to Resolution or Improvement of Signs and Symptoms of cUTI and AP Present a Baseline in the Micro-ITT Populations

End point description:

Time (days) to resolution or improvement of signs and symptoms of cUTI and AP present at baseline was defined as follows: date of the first visit at which all baseline signs/symptoms have improved by at least 1 grade with worsening of none and development of no new signs/symptoms of the index infection minus the date of randomization. Micro-ITT population included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens.

End point type	Secondary

End point timeframe:

Day 25 (LFU)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: days				
arithmetic mean (standard deviation)	4.1 (± 3.85)	3.7 (± 3.26)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TBPM-PI-HBr 600 mg v Ertapenem 1g
Number of subjects included in analysis	868
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.044
Method	Logrank

Secondary: Time (Days) to Defervescence in Micro-ITT Population With a Documented Fever at Screening or Day 1

End point title	Time (Days) to Defervescence in Micro-ITT Population With a Documented Fever at Screening or Day 1

End point description:

Time to Defervescence (days) = date of first post-baseline temperature measure with maximum daily temperature ≤38°C at the date of randomization. Micro-ITT population included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens. Overall number of subjects analysed are the subjects with data available for analysis.

End point type	Secondary
End point timeframe: Day 25 (LFU)	

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	193		
Units: days				
arithmetic mean (standard deviation)	2.2 (± 1.33)	2.2 (± 1.40)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ertapenem 1g v TBPM-PI-HBr 600 mg
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.736
Method	Logrank

Secondary: Rate of Clinical Relapse at the LFU in the Micro-ITT Population

End point title	Rate of Clinical Relapse at the LFU in the Micro-ITT Population
End point description: Clinical relapse is subjects who met criteria for clinical cure at TOC, but new signs and symptoms of cUTI or AP are present at the LFU Visit and the subject requires antibiotic therapy for the cUT. Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted. Micro-ITT population included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens.	
End point type	Secondary
End point timeframe: Day 25 (LFU)	

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: percentage of subjects				
number (not applicable)	2.7	3.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Rates of Superinfection And New Infection In The Micro-ITT Population

End point title	Rates of Superinfection And New Infection In The Micro-ITT Population

End point description:

Superinfection was isolation of a new uropathogen at ≥10^5 CFU/mL (other than original Baseline pathogen from blood and/or urine) from a urine culture that was accompanied by clinical signs and symptoms of infection requiring alternative antimicrobial therapy (e.g., the participant was assessed by the investigator as a clinical failure) during the period up to and including EOT. New infection was isolation of new uropathogen at ≥105 CFU/mL (other than the original baseline pathogen from blood and/or urine) from a urine culture that was accompanied by clinical signs symptoms of infection requiring alternative antimicrobial therapy in the period after EOT. Micro-ITT population included all randomized subjects with a confirmed diagnosis of cUTI or AP and a positive Screening urine culture defined as growth of one or two uropathogens at ≥10^5 CFU/mL and/or positive Screening blood culture with isolation of one or more uropathogens.

End point type	Secondary

End point timeframe:

Day 25 (LFU)

End point values	TBPM-PI-HBr 600 mg	Ertapenem 1g		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	419		
Units: percentage of subjects				
number (not applicable)				
Superinfection	0.2	2.1		
New Infection	1.1	1.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vss) at Steady State in TBPM-PI-HBr Recipients in the PK Population

End point title	Apparent Volume of Distribution (Vss) at Steady State in TBPM-PI-HBr Recipients in the PK Population[3]

End point description:

PK population included subjects treated with at least 1 dose of TBPM-PI-HBr with at least 1 analyzable plasma or urine PK sample.

End point type	Secondary

End point timeframe:

Predose and post-dose at 0.25h, 0.5h, 1h, 2h, and 8h on Days 1 and 3

Notes:

[3] - 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: No statistical analyses have been specified for this end point.

End point values	TBPM-PI-HBr 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Litre (L)				
arithmetic mean (full range (min-max))				
Day 1	75.5 (49.5 to 89.9)			
Day 3	75.5 (49.5 to 89.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax in TBPM-PI-HBr Recipients in the PK Population

End point title	Cmax in TBPM-PI-HBr Recipients in the PK Population[4]

End point description:

PK population included subjects treated with at least 1 dose of TBPM-PI-HBr with at least 1 analyzable plasma or urine PK sample. The data is reported only for TBPM-PI-HBr arm.

End point type	Secondary

End point timeframe:

Predose and post-dose at 0.25h, 0.5h, 1h, 2h, and 8h on Days 1 and 3

Notes:

[4] - 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: No statistical analyses have been specified for this end point.

End point values	TBPM-PI-HBr 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: microgram per milliliter (µg/mL)				
arithmetic mean (full range (min-max))				
Day 1	7.01 (2.05 to 17.2)			
Day 3	7.21 (2.11 to 18.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Curve (AUC 0-24) in TBPM-PI-HBr Recipients in the PK Population

End point title	Area Under Curve (AUC 0-24) in TBPM-PI-HBr Recipients in the PK Population[5]

End point description:

PK population included subjects treated with at least 1 dose of TBPM-PI-HBr with at least 1 analyzable plasma or urine PK sample. The data is reported only for TBPM-PI-HBr arm.

End point type	Secondary

End point timeframe:

Predose and post-dose on Day 1 and 3 at 1 h; 4h (±1h); and 8 h prior to the next scheduled dose

Notes:

[5] - 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: No statistical analyses have been specified for this end point.

End point values	TBPM-PI-HBr 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: microgram.hour per milliliter (µg•h/mL)				
arithmetic mean (full range (min-max))				
Day 1	65.5 (27.6 to 243)			
Day 2	74.6 (27.6 to 318)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Concentration (Cmin) in TBPM-PI-HBr Recipients in the PK Population

End point title	Minimum Concentration (Cmin) in TBPM-PI-HBr Recipients in the PK Population[6]

End point description:

PK population included subjects treated with at least 1 dose of TBPM-PI-HBr with at least 1 analyzable plasma or urine PK sample. The data is reported only for TBPM-PI-HBr arm.

End point type	Secondary

End point timeframe:

Predose and post-dose at 0.25h, 0.5h, 1h, 2h, and 8h on Days 1 and 3

Notes:

[6] - 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: No statistical analyses have been specified for this end point.

End point values	TBPM-PI-HBr 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: µg/mL				
arithmetic mean (full range (min-max))				

Day 1	0.706 (0.000913 to 4.89)			
Day 3	1.17 (0.000877 to 8.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic Clearance (CL) in TBPM-PI-HBr Recipients in the PK Population

End point title	Systemic Clearance (CL) in TBPM-PI-HBr Recipients in the PK Population[7]

End point description:

PK population included subjects treated with at least 1 dose of TBPM-PI-HBr with at least 1 analyzable plasma or urine PK sample. The data is reported only for TBPM-PI-HBr arm.

End point type	Secondary

End point timeframe:

Predose and post-dose at 0.25h, 0.5h, 1h, 2h, and 8h on Days 1 and 3

Notes:

[7] - 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: No statistical analyses have been specified for this end point.

End point values	TBPM-PI-HBr 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Litre per hour (L/h)				
arithmetic mean (full range (min-max))				
Day 1	31.6 (5.65 to 65.3)			
Day 3	31.6 (5.65 to 65.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of administration up to Day 25 post-treatment ± 2 days (up to approximately 27 days)

Adverse event reporting additional description:

Safety analysis population included all randomized participants who received any amount of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	TBPM-PI-HBr 600 mg

Reporting group description:

TBPM-PI-HBr 600 mg (300 mg × 2) film-coated tablets, administered orally three times per day (every 8 hours [q8h] ± 0.5 h) plus a single dummy IV infusion over 30 minutes (min) once daily (every 24 hours [q24h] ± 0.5 h) up to Day 15; participants with moderate renal insufficiency (creatinine clearance [CrCl] >30 to ≤50 mL/min) required TBPM-PI-HBr dosage adjustment to 300 mg (one tablet) q8h ± 0.5 h.

Reporting group title	Ertapenem 1 g

Reporting group description:

Ertapenem for IV injection, administered as a 1-gram IV infusion over 30 min once daily (q24h ± 0.5 h) plus dummy placebo tablets administered orally q8h (±0.5 h) up to Day 14; no dose adjustment of ertapenem was required for participants with renal insufficiency.

Serious adverse events	TBPM-PI-HBr 600 mg	Ertapenem 1 g	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 687 (2.04%)	12 / 685 (1.75%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Clostridium test positive			
subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural pneumothorax			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Myocardial ischaemia			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (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			
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 687 (0.15%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			

subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis acute			
subjects affected / exposed	1 / 687 (0.15%)	2 / 685 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 687 (0.00%)	1 / 685 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 687 (0.15%)	0 / 685 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TBPM-PI-HBr 600 mg	Ertapenem 1 g	
Total subjects affected by non-serious adverse events subjects affected / exposed	39 / 687 (5.68%)	30 / 685 (4.38%)	
Gastrointestinal disorders Diarrohea subjects affected / exposed	39 / 687 (5.68%)	30 / 685 (4.38%)	
occurrences (all)	40	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2019	Amendment 1: Additional information regarding the total anticipated enrollment of subjects was contingent on sufficient number of evaluable subjects. Subjects with moderate renal impairment were included with dosage adjustments. Inclusion Criterion 3 was added as additional criteria for subjects presenting with nausea and/or vomiting. Clarification of subjects populations and evaluability rates. Statement added that the planned total enrollment may be adjusted as needed to ensure sufficient data were available from 884 evaluable subjects if a change in dose was required. Clarification on reasons for IP discontinuation and subsequent EOT assessment. Additional detail were added for comparator (ertapenem) and placebo. Additional instructions were added regarding timing of IP administration, timing of IP oral medication, dosing interruptions, and missed doses. Clarification of CrCl monitoring and the process for recording the unblinding of source documents. Definition of Clinical Cure and Microbiological Eradication were updated to specify that subjects must be alive to qualify. Permitted concomitant medications were updated to include antiemetic. Clarification that Day 1 laboratory data did not need to be repeated if the Screening central safety laboratory data were collected on Day 1.
25 February 2019	Amendment 2: Corrections in grammar made throughout document as necessary. Additional information regarding the total anticipated enrollment of subjects is contingent on sufficient number of evaluable subjects. Subjects with moderate renal insufficiency (CrCl >30 to <50 mL/min) will require TBPM-PI-HBr dosage adjustment to 300 mg q8h. Plasma PK Assessments: Updated to collect blood samples on Day 2 following an oral dose (first, second or third), instead of Day 1 / First Dose. Updated to collect blood samples on Day 2 following an oral dose (first, second or third), instead of Day 1 / First Dose. Increased the number of PK samples collected from two (1 h and 6 h) to three (1, 4 and 8 h). Subjects with moderate renal insufficiency (CrCl >30 to <50 mL/min) will require TBPM-PI-HBr dosage adjustment to 300 mg q8h OR 1 dummy oral tablet q8h. Added that a decline in post-baseline renal function such that the estimated CrCl falls to <30 mL/min is possible reason for premature discontinuation from IP. Timing of Dose Administration. Subjects prematurely discontinued from IP for safety reasons and who require further antibacterial therapy for the cUTI/AP should be assessed as a clinical and microbiological failure at EOT and TOC. Definition of Clinical Cure was updated to specify that subjects must be alive to qualify. Subjects deemed clinical failures at EOT or TOC should be considered for further diagnostic workup, including urinary tract imaging (e.g., ultrasound), to assess for undiagnosed anatomical, obstructive, or neurogenic abnormalities, according to the best clinical judgment of the Investigator was added. Definition of Microbiologic eradication was updated to specify that subjects must be alive to qualify. Definition of sustained microbiologic eradication was updated to include requirements of no subsequent urine culture after TOC demonstrating recurrence of the original baseline uropathogen.

26 May 2020	Amendment 3: The intent of this criterion is to exclude HIV-positive subjects at risk for opportunistic infections (e.g., with AIDS or CD4 count <200 within the past year) Exclusion criteria updated accordingly to reflect this clarification. Specified that EOT ECG's must be performed on day of last dose, not the following day as allowed for other EOT assessments. Clarification was added for Standard-of-care assessments performed at the site within the Screening period (within 24 hours of randomization) may be used to determine subject eligibility even if performed prior to signing the informed consent form (ICF). For example, the Schedule of Assessments Table notes that "urine cultures collected per standard-of-care up to 24 h prior to randomization may be used for eligibility". Other routine clinical assessments may be used to determine eligibility if performed prior to informed consent but within the 24-hour Screening period, Screening Visit and Day 1 occur on the same day the focused physical exam on Day 1 are optional, clarification was added for SAE. The prolongation of hospitalization criterion is based on best clinical judgment of the Principal Investigator. For the purposes of this study, duration of intended hospitalization at the time of study randomization may be reasonably presumed to be approximately 14 days, as this is the maximum allowed duration of study drug. Therefore, cases of clinical failure leading to prolongation of hospitalization beyond approximately 14 days should be evaluated for the potential of meeting SAE criteria. The Medical Monitor should be contacted if help is needed in determining reportability of a potential SAE. Non-inferiority margin changed from -10% to -12.5%; added text summarizing rationale for change in non-inferiority margin. Added that aliquots should be collected "after the first dose of the study drug".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported