

**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

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|--|----|
| 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 $\geq 10^5$ 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 $\geq 10^5$ 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 <10³ 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 ≥10⁵ 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 \pm 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 met 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 $\geq 10^5$ 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 $\geq 10^5$ 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 $\geq 10^5$ 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: | |
| <p>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 $\geq 10^5$ 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.</p> | |
| 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, <i>Citrobacter braakii</i> (n=0, 2) | 0.0 | 100 | | |
| Enterobacterales, <i>Citrobacter freundii</i> (n=4, 3) | 75.0 | 66.7 | | |
| Enterobacterales, <i>Citrobacter koseri</i> (n=3, 4) | 100 | 100 | | |
| Enterobacterales, <i>Enterobacter amnigenus</i> (n=0, 1) | 0.0 | 100 | | |
| Enterobacterales, <i>Enterobacter asburiae</i> (n=0, 1) | 0.0 | 100 | | |
| Enterobacterales, <i>Enterobacter bugandensis</i> (n=0, 1) | 0.0 | 100 | | |
| Enterobacterales, <i>Enterobacter cloacae</i> (n=11, 8) | 90.9 | 100 | | |
| Enterobacterales, <i>Escherichia coli</i> (n=287, 270) | 98.3 | 96.7 | | |
| Enterobacterales, <i>Klebsiella aerogenes</i> (n=1, 1) | 100 | 0.0 | | |
| Enterobacterales, <i>Klebsiella oxytoca</i> (n=4, 3) | 100 | 100 | | |
| Enterobacterales, <i>Klebsiella pneumoniae</i> (n=53, 71) | 98.1 | 98.6 | | |
| Enterobacterales, <i>Klebsiella variicola</i> (n=2, 4) | 100 | 100 | | |
| Enterobacterales, <i>Morganella morganii</i> (n=2, 4) | 100 | 100 | | |
| Enterobacterales, <i>Proteus hauseri</i> (n=2, 0) | 100 | 0.0 | | |
| Enterobacterales, <i>Proteus mirabilis</i> (n=35, 23) | 97.1 | 100 | | |
| Enterobacterales, <i>Proteus penneri</i> (n=0, 1) | 0.0 | 100 | | |
| Enterobacterales, <i>Proteus vulgaris</i> (n=0, 1) | 0.0 | 100 | | |
| Enterobacterales, <i>Providencia rettgeri</i> (n=4, 3) | 100 | 100 | | |
| Enterobacterales, <i>Providencia stuartii</i> (n=1, 1) | 100 | 100 | | |
| Enterobacterales, <i>Raoultella ornithinolytica</i> (n=2, 0) | 100 | 0.0 | | |
| Enterobacterales, <i>Serratia liquefaciens</i> (n=0, 1) | 0.0 | 100 | | |
| Enterobacterales, <i>Serratia marcescens</i> (n=4, 2) | 100 | 100 | | |
| Gram Positive, <i>Enterococcus faecalis</i> (n=58, 36) | 94.8 | 91.7 | | |
| Gram Positive, <i>Enterococcus faecium</i> (n=5, 2) | 100 | 100 | | |
| Gram Positive, <i>Enterococcus hirae</i> (n=1, 0) | 100 | 0.0 | | |
| Gram Positive, <i>Staphylococcus aureus</i> (n=5, 8) | 100 | 75.0 | | |
| Gram Positive, <i>Staphylococcus lugdunensis</i> (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 $\geq 10^5$ 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 $\geq 10^5$ 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 $\geq 10^5$ 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 $\geq 10^5$ 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 $\geq 10^5$ 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 $\geq 10^5$ 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 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 $\geq 10^5$ 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 $\geq 10^5$ 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 $\geq 10^5$ 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 (\pm 3.85) | 3.7 (\pm 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 $\leq 38^\circ\text{C}$ 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 $\geq 10^5$ 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 cUTI. 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 $\geq 10^5$ 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 $\geq 10^5$ 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 $\geq 10^5$ 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 $\geq 10^5$ 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 (± 1 h); 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 ($\mu\text{g}\cdot\text{h/mL}$) | | | | |
| 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: $\mu\text{g/mL}$ | | | | |
| 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 \pm 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 \times 2) film-coated tablets, administered orally three times per day (every 8 hours [q8h] \pm 0.5 h) plus a single dummy IV infusion over 30 minutes (min) once daily (every 24 hours [q24h] \pm 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 \pm 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 \pm 0.5 h) plus dummy placebo tablets administered orally q8h (\pm 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 | | | |
| Diarrhea | | | |
| 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 | <p>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.</p> |
| 25 February 2019 | <p>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.</p> |

| | |
|-------------|--|
| 26 May 2020 | <p>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".</p> |
|-------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported