# Clinical trial results:
# A Randomized, Double-blind, Multi-center Study to Establish the Efficacy and Safety of Ceftobiprole Medocaril Compared to Daptomycin in the Treatment of Staphylococcus Aureus Bacteremia, Including Infective Endocarditis

## Summary

| | |
|---|---|
| EudraCT number | 2017-001699-43 |
| Trial protocol | DE HU BG ES IT GR PT |
| Global end of trial date | 11 March 2022 |

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 28 March 2023 |
| First version publication date | 28 March 2023 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BPR-CS-009 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03138733 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND number: 64,407 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Basilea Pharmaceutica International Ltd, Allschwil |
| Sponsor organisation address | Hegenheimermattweg 167b, Allschwil, Switzerland, 4123 |
| Public contact | Dr Marc Engelhardt, MD, Basilea Pharmaceutica International Ltd, Allschwil, +41 797010551, marc.engelhardt@basilea.com |
| Scientific contact | Dr Marc Engelhardt, MD, Basilea Pharmaceutica International Ltd, Allschwil, +41 797010551, marc.engelhardt@basilea.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 20 June 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 March 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the non-inferiority of ceftobiprole to daptomycin for overall success as assessed by an independent Data Review Committee (DRC) in the treatment of Staphylococcus aureus bacteremia (SAB), including infective endocarditis (IE), at the post-treatment evaluation (PTE) visit in the modified Intent-to-Treat (mITT) population.

Protection of trial subjects:

An independent DSMB was commissioned by the sponsor to, among other things, ensure the safety of the patients in the study.

Background therapy:

None

Evidence for comparator:

The comparator, daptomycin is the only antibacterial treatment licensed for SAB including IE that provides similar bactericidal activity against both Methicillin-susceptible Staphylococcus aureus (MSSA) and Methicillin-resistant Staphylococcus aureus (MRSA) as the investigational product.

| | |
|---|---|
| Actual start date of recruitment | 26 August 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Israel: 22 |
| Country: Number of subjects enrolled | Georgia: 47 |
| Country: Number of subjects enrolled | Russian Federation: 34 |
| Country: Number of subjects enrolled | Turkey: 4 |
| Country: Number of subjects enrolled | Argentina: 5 |
| Country: Number of subjects enrolled | Colombia: 2 |
| Country: Number of subjects enrolled | Mexico: 5 |
| Country: Number of subjects enrolled | Panama: 1 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | United States: 10 |
| Country: Number of subjects enrolled | Ukraine: 181 |
| Country: Number of subjects enrolled | Bulgaria: 56 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Greece: 1 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Serbia: 5 |

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 6 |
| Worldwide total number of subjects | 390 |
| EEA total number of subjects | 70 |

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) | 268 |
| From 65 to 84 years | 116 |
| 85 years and over | 6 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment started on 26 August 2018 and ended on 6 January 2022. Hospitalized male or female patients aged ≥ 18 years were recruited who had SAB, based on ≥ 1 positive blood culture obtained within 72 h prior to randomization, with signs or symptoms of bloodstream infection.

### Pre-assignment

Screening details:

A total of 390 patients comprised the Intent-to-Treat (ITT) population. Three of these patients were excluded from the modified ITT population: one patient who discontinued prior to receiving study treatment, and two patients who were determined not to have a confirmed positive blood culture for S.aureus at baseline

### Period 1

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

Blinding implementation details:

Patients in the ceftobiprole group received dummy infusions with placebo (physiological saline, 0.9% NaCl) matching the daptomycin schedule, and patients in the daptomycin group received dummy infusions with placebo (physiological saline, 0.9% NaCl) matching the ceftobiprole schedule.
When aztreonam was required as add-on therapy in the daptomycin treatment arm, the corresponding treatment group in the ceftobiprole arm received dummy treatment with placebo.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ceftobiprole |

Arm description:

Ceftobiprole 500 mg (as 667 mg ceftobiprole medocaril) was administered as a 2-hour infusion

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ceftobiprole medocaril |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, a cephalosporin which has been developed for i.v. administration. Ceftobiprole medocaril was supplied as lyophilized powder in bottles to be reconstituted and diluted for administration via infusion in a hospital setting. Ceftobiprole medocaril was provided in packs of 10 vials.
For patients with normal to mildly-impaired renal function (CLCR ≥ 50 mL/min), from Day 1 up to and including Day 8, ceftobiprole 500 mg was administered as a 2 hour i.v. infusion every 6 hours. From Day 9 until the end of treatment, ceftobiprole 500 mg was administered as a 2 hour i.v. infusion every 8 hours. Schedule adjustments were made for patients with renal impairment (CLCR < 50 mL/min).

| | |
|---|---|
| **Arm title** | Daptomycin |

Arm description:

Daptomycin 6 mg/kg (up to 10 mg/kg based on institutional standards) was administered as a 0.5-hour infusion, with or without aztreonam

| | |
|---|---|
| Arm type | Active comparator |

| | |
|---|---|
| Investigational medicinal product name | Daptomycin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Daptomycin weight-based at 6 mg/kg (up to 10 mg/kg in accordance with institutional standards) administered as 0.5 hour i.v. infusion every 24 hours (with schedule adjusted in patients with renal impairment).

| **Number of subjects in period 1** | Ceftobiprole | Daptomycin |
|---|---|---|
| Started | 192 | 198 |
| Completed | 157 | 169 |
| Not completed | 35 | 29 |
| Adverse event, serious fatal | 17 | 18 |
| Consent withdrawn by subject | 11 | 6 |
| Adverse event, non-fatal | 1 | - |
| The patient was transferred to another hospital | 1 | - |
| Administrative or logistical reason | 1 | - |
| Lost to follow-up | 3 | 2 |
| Protocol deviation | 1 | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ceftobiprole |
| Reporting group description: | |
| Ceftobiprole 500 mg (as 667 mg ceftobiprole medocaril) was administered as a 2-hour infusion | |
| Reporting group title | Daptomycin |
| Reporting group description: | |
| Daptomycin 6 mg/kg (up to 10 mg/kg based on institutional standards) was administered as a 0.5-hour infusion, with or without aztreonam | |

| Reporting group values | Ceftobiprole | Daptomycin | Total |
|---|---|---|---|
| Number of subjects | 192 | 198 | 390 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 133 | 135 | 268 |
| From 65-84 years | 57 | 59 | 116 |
| 85 years and over | 2 | 4 | 6 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.6 | 56.5 | |
| standard deviation | ± 15.11 | ± 15.33 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 61 | 58 | 119 |
| Male | 131 | 140 | 271 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 14 | 15 | 29 |
| Not Hispanic or Latino | 177 | 182 | 359 |
| Unknown or Not Reported | 1 | 1 | 2 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 1 | 1 | 2 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 4 | 5 | 9 |
| White | 182 | 192 | 374 |
| Unknown or Not Reported | 4 | 0 | 4 |
| Baseline categories related to SAB | | | |
| Units: Subjects | | | |
| No SAB or no complicated SAB | 3 | 0 | 3 |

| | | | |
|---|---|---|---|
| Complicated SAB with endocarditis | 19 | 13 | 32 |
| Complicated SAB without endocarditis | 170 | 185 | 355 |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | Ceftobiprole mITT |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The mITT (Intent-to-Treat population who received any dose of study medication) and who had a blood culture positive for staphylococcus aureus represented the Baseline Analysis Population. It comprised 387 out of the 390 patients in the ITT population.

| | |
|---|---|
| Subject analysis set title | Daptomycin mITT |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The mITT (Intent-to-Treat population who received any dose of study medication) and who had a blood culture positive for staphylococcus aureus represented the Baseline Analysis Population. It comprised 387 out of the 390 patients in the ITT population.

| | |
|---|---|
| Subject analysis set title | Ceftobiprole CE |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The CE population comprised the subset of patients in the mITT population who complied with important pre-specified aspects of the study

| | |
|---|---|
| Subject analysis set title | Daptomycin CE |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The Clinically Evaluable (CE) population comprised the subset of patients in the mITT population who complied with important pre-specified aspects of the study

| | |
|---|---|
| Subject analysis set title | Ceftobiprole safety analysis population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety population comprised all randomized patients who received any dose of study drug. Patients in the Safety population were analyzed according to the first study drug received.

| | |
|---|---|
| Subject analysis set title | Daptomycin safety analysis population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety population comprised all randomized patients who received any dose of study drug. Patients in the Safety population were analyzed according to the first study drug received.

| **Reporting group values** | Ceftobiprole mITT | Daptomycin mITT | Ceftobiprole CE |
|---|---|---|---|
| Number of subjects | 189 | 198 | 163 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 131 | 135 | |
| From 65-84 years | 56 | 59 | |
| 85 years and over | 2 | 4 | |

| | | | |
|---|---|---|---|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.5 | 56.5 | |
| standard deviation | ± 15.18 | ± 15.33 | ± |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 61 | 58 | |
| Male | 128 | 140 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 14 | 15 | |
| Not Hispanic or Latino | 174 | 182 | |
| Unknown or Not Reported | 1 | 1 | |
| Race | | | |
| Units: Subjects | | | |
| Asian | 1 | 1 | |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | |
| Black or African American | 4 | 5 | |
| White | 179 | 192 | |
| Unknown or Not Reported | 4 | 0 | |
| Baseline categories related to SAB | | | |
| Units: Subjects | | | |
| No SAB or no complicated SAB | 0 | 0 | |
| Complicated SAB with endocarditis | 19 | 13 | |
| Complicated SAB without endocarditis | 170 | 185 | |

| **Reporting group values** | Daptomycin CE | Ceftobiprole safety analysis population | Daptomycin safety analysis population |
|---|---|---|---|
| Number of subjects | 167 | 191 | 198 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | ± |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | | | |
| Male | | | |

| | | | |
|---|---|---|---|
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino<br>Not Hispanic or Latino<br>Unknown or Not Reported | | | |
| Race<br>Units: Subjects | | | |
| Asian<br>Native Hawaiian or Other Pacific Islander<br>Black or African American<br>White<br>Unknown or Not Reported | | | |
| Baseline categories related to SAB<br>Units: Subjects | | | |
| No SAB or no complicated SAB<br>Complicated SAB with endocarditis<br>Complicated SAB without endocarditis | | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Ceftobiprole |

Reporting group description:

Ceftobiprole 500 mg (as 667 mg ceftobiprole medocaril) was administered as a 2-hour infusion

| | |
|---|---|
| Reporting group title | Daptomycin |

Reporting group description:

Daptomycin 6 mg/kg (up to 10 mg/kg based on institutional standards) was administered as a 0.5-hour infusion, with or without aztreonam

| | |
|---|---|
| Subject analysis set title | Ceftobiprole mITT |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The mITT (Intent-to-Treat population who received any dose of study medication) and who had a blood culture positive for staphylococcus aureus represented the Baseline Analysis Population. It comprised 387 out of the 390 patients in the ITT population.

| | |
|---|---|
| Subject analysis set title | Daptomycin mITT |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The mITT (Intent-to-Treat population who received any dose of study medication) and who had a blood culture positive for staphylococcus aureus represented the Baseline Analysis Population. It comprised 387 out of the 390 patients in the ITT population.

| | |
|---|---|
| Subject analysis set title | Ceftobiprole CE |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The CE population comprised the subset of patients in the mITT population who complied with important pre-specified aspects of the study

| | |
|---|---|
| Subject analysis set title | Daptomycin CE |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The Clinically Evaluable (CE) population comprised the subset of patients in the mITT population who complied with important pre-specified aspects of the study

| | |
|---|---|
| Subject analysis set title | Ceftobiprole safety analysis population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety population comprised all randomized patients who received any dose of study drug. Patients in the Safety population were analyzed according to the first study drug received.

| | |
|---|---|
| Subject analysis set title | Daptomycin safety analysis population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety population comprised all randomized patients who received any dose of study drug. Patients in the Safety population were analyzed according to the first study drug received.

### Primary: Overall Success at the Post-treatment Evaluation (PTE) Visit

| | |
|---|---|
| End point title | Overall Success at the Post-treatment Evaluation (PTE) Visit |

End point description:

Comparison of overall success rates in the mITT population
Overall success at PTE for the mITT population was defined as all of the following criteria being met (Responder):
Patient alive at Day 70 (± 5 days) post-randomization.
No new metastatic foci or complications of the SAB infection.
Resolution or improvement of SAB-related clinical signs and symptoms.
Two negative blood cultures for S. aureus (without any subsequent positive blood culture for S. aureus)

| | |
|---|---|
| End point type | Primary |

End point timeframe:

PTE visit on Day 70 (± 5 days) post-randomization

| End point values | Ceftobiprole mITT | Daptomycin mITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 189 | 198 | | |
| Units: Subjects | | | | |
| Number of responders | 132 | 136 | | |
| Number of non-responders | 57 | 62 | | |

### Statistical analyses

| Statistical analysis title | Non-inferiority test in the mITT population |
|---|---|

Statistical analysis description:

The observed difference in percentage of responders at PTE (ceftobiprole group minus the daptomycin group) were determined and a two-sided 95% confidence interval (CI) for the observed difference was computed, with adjustment for actual stratum (dialysis status and prior antibacterial treatment use). Cochran-Mantel-Haenszel (CMH) weights were used for the stratum weight in the calculation of the CI

| | |
|---|---|
| Comparison groups | Ceftobiprole mITT v Daptomycin mITT |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| P-value | < 0.025 [2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Adjusted proportion difference |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.1 |
| upper limit | 11.1 |

Notes:

[1] - The non-inferiority hypothesis test was a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the two sided 95% CI for the difference in response rates in the mITT population was greater than −15%, the non-inferiority of ceftobiprole to daptomycin therapy was to be concluded.

[2] - This was a one-sided test including adjustment factors: dialysis status and prior antibacterial treatment use

## Secondary: Overall Success at the PTE Visit in the CE Population

| End point title | Overall Success at the PTE Visit in the CE Population |
|---|---|

End point description:

Comparison of overall success rates in the CE population
Overall success at PTE for the CE population was defined as all of the following criteria being met (Responder):
Patient alive at Day 70 (± 5 days) post-randomization
No new metastatic foci or complications of the SAB infection
Resolution or improvement of SAB-related clinical signs and symptoms
Two negative blood cultures for S. aureus (without any subsequent positive blood culture for S. aureus)

| End point type | Secondary |
|---|---|

End point timeframe:

At PTE visit on Day 70 (± 5 days) post-randomization

| End point values | Ceftobiprole CE | Daptomycin CE | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 163 | 167 | | |
| Units: Subjects | | | | |
| Number of responders | 127 | 130 | | |
| Number of non-responders | 36 | 37 | | |

**Statistical analyses**

| Statistical analysis title | Descriptive statistics |
|---|---|
| Comparison groups | Ceftobiprole CE v Daptomycin CE |
| Number of subjects included in analysis | 330 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted proportion difference |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.3 |
| upper limit | 9.5 |

## Secondary: Microbiological Eradication at the PTE Visit

| End point title | Microbiological Eradication at the PTE Visit |
|---|---|

End point description:

Comparison of microbiological eradication rates in the mITT population. Microbiological eradication rate was defined as a negative blood culture for S. aureus during study treatment and another negative blood culture during the follow up period up to PTE.

| End point type | Secondary |
|---|---|

End point timeframe:

At PTE visit on Day 70 (± 5 days) post-randomization

| End point values | Ceftobiprole mITT | Daptomycin mITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 189 | 198 | | |
| Units: Subjects | | | | |
| Subjects with microbiological eradication | 155 | 153 | | |

**Statistical analyses**

| **Statistical analysis title** | Descriptive statistics |
|---|---|
| Comparison groups | Ceftobiprole mITT v Daptomycin mITT |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted proportion difference |
| Point estimate | 5.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.9 |
| upper limit | 13 |

| **Secondary: All-cause Mortality at the PTE Visit** | |
|---|---|
| End point title | All-cause Mortality at the PTE Visit |
| End point description:<br>Comparison of all-cause mortality rates in the mITT population | |
| End point type | Secondary |
| End point timeframe:<br>At PTE visit on Day 70 (± 5 days) post-randomization | |

| **End point values** | Ceftobiprole mITT | Daptomycin mITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 189 | 198 | | |
| Units: Subjects | | | | |
| Subjects died | 17 | 18 | | |
| Subjects alive | 172 | 180 | | |

**Statistical analyses**

| **Statistical analysis title** | Descriptive statistics |
|---|---|
| Comparison groups | Ceftobiprole mITT v Daptomycin mITT |

| | |
|---|---|
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted proportion difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.2 |
| upper limit | 5.2 |

## Secondary: Development of New Metastatic Foci or Other Complications of SAB After Day 7

| | |
|---|---|
| End point title | Development of New Metastatic Foci or Other Complications of SAB After Day 7 |

End point description:

Comparison of complication rates in the mITT population defined by number of patients with development of new metastatic foci or other complications of SAB after Day 7

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Assessment after Day 7 post-randomization through to post-treatment evaluation (PTE) visit on Day 70 (± 5 days)

| End point values | Ceftobiprole mITT | Daptomycin mITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 189 | 198 | | |
| Units: Subjects | | | | |
| Subjects with development of new metastatic foci o | 11 | 11 | | |
| Subjects without development of new metastatic foc | 178 | 187 | | |

### Statistical analyses

| Statistical analysis title | Descriptive statistics |
|---|---|
| Comparison groups | Ceftobiprole mITT v Daptomycin mITT |
| Number of subjects included in analysis | 387 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted proportion difference |
| Point estimate | 0.1 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.6 |
| upper limit | 4.8 |

## Secondary: Time to Staphylococcus Aureus Bloodstream Clearance

| End point title | Time to Staphylococcus Aureus Bloodstream Clearance |
|---|---|

End point description:

Time-to-event in the mITT Bloodstream clearance was defined as two consecutive study days with blood-culture-negative assessments for S. aureus, without any subsequent S. aureus relapse or reinfection.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 6 weeks post-randomization

| End point values | Ceftobiprole mITT | Daptomycin mITT | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 189 | 198 | | |
| Units: Time | | | | |
| median (confidence interval 95%) | | | | |
| Time to S. Aureus Bloodstream Clearance | 4 (3 to 5) | 4 (3 to 5) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overview of Adverse Events (AEs)

| End point title | Overview of Adverse Events (AEs) |
|---|---|

End point description:

Overview of Adverse Events (AEs)

| End point type | Secondary |
|---|---|

End point timeframe:

AEs were assessed from the first dose of study drug through the post-treatment evaluation (PTE) visit on Day 70 (± 5 days)

| End point values | Ceftobiprole safety analysis population | Daptomycin safety analysis population | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 191 | 198 | | |
| Units: Subjects | | | | |
| Any adverse events (AEs) | 121 | 117 | | |
| Any drug-related AE | 25 | 11 | | |
| Any severe AEs | 29 | 38 | | |
| Any study drug-related severe AEs | 1 | 2 | | |
| Any serious adverse events (SAE) | 36 | 45 | | |
| Any drug-related SAEs | 2 | 4 | | |
| Any AE leading to treat. discont. | 18 | 18 | | |
| Study drug-related AEs leading to treat. discont. | 9 | 3 | | |
| Any AE leading to death | 17 | 18 | | |
| Study drug-related AEs leading to death | 0 | 0 | | |
| Any AE of special interest (AESI) | 9 | 7 | | |
| Any drug-related AESI | 5 | 4 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| From first administration of study medication up to 30 days after the last administration. | |
| Adverse event reporting additional description: | |
| Treatment-emergent adverse events and serious adverse events | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Daptomycin |
| Reporting group description: | |
| Daptomycin | |
| Reporting group title | Ceftobiprole |
| Reporting group description: | |
| Ceftobiprole medocaril | |

| Serious adverse events | Daptomycin | Ceftobiprole | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 45 / 198 (22.73%) | 36 / 191 (18.85%) | |
| number of deaths (all causes) | 18 | 17 | |
| number of deaths resulting from adverse events | 18 | 17 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chloroma | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Surgical and medical procedures | | | |
| Leg amputation | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 4 / 191 (2.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 2 / 191 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eosinophilic pneumonia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 2 / 191 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Eosinophilic pneumonia acute | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 2 / 191 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Investigations | | | |
| Wound healing normal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney rupture | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemodialysis complication | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Angina unstable | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intracardiac mass | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Myocardial infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemic seizure | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

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|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocoagulable state | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intra-abdominal haemorrhage | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic haemorrhage | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis necrotising | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| 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 | | | |
| Cutaneous vasculitis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pemphigoid | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (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 | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal haematoma | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Myopathy | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Infections and infestations** | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 2 / 191 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Candida sepsis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Endocarditis staphylococcal | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma infection | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral discitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 198 (1.01%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mediastinitis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle abscess | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psoas abscess | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 198 (1.01%) | 3 / 191 (1.57%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Osteomyelitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic necrosis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Purulent pericarditis | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 8 / 198 (4.04%) | 4 / 191 (2.09%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 2 | |
| Skin bacterial infection | | | |
| subjects affected / exposed | 0 / 198 (0.00%) | 1 / 191 (0.52%) | |
| 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 / 198 (0.51%) | 1 / 191 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superinfection bacterial | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 198 (0.51%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 3 / 198 (1.52%) | 0 / 191 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Daptomycin | Ceftobiprole | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 198 (22.73%) | 61 / 191 (31.94%) | |
| Investigations | | | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 5 / 198 (2.53%) | 17 / 191 (8.90%) | |
| occurrences (all) | 8 | 19 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 15 / 198 (7.58%) | 12 / 191 (6.28%) | |
| occurrences (all) | 15 | 12 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 24 / 198 (12.12%) | 20 / 191 (10.47%) | |
| occurrences (all) | 27 | 21 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 198 (2.53%) | 13 / 191 (6.81%) | |
| occurrences (all) | 5 | 14 | |
| Nausea | | | |
| subjects affected / exposed | 8 / 198 (4.04%) | 20 / 191 (10.47%) | |
| occurrences (all) | 12 | 22 | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 198 (2.02%) | 16 / 191 (8.38%) | |
| occurrences (all) | 4 | 18 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 05 April 2019 | • Reduction of the number of required signs and symptoms<br>• Vital signs and laboratory tests obtained prior to informed consent<br>• Addition of ±3 days to visits on Day 35 and Day 42<br>• Discontinuation of treatment if S. aureus has reduced susceptibility<br>• Restriction of Gram-negative treatment blinding to active treatment<br>• Continuation of contraception until 7 days after last dose<br>• Change in frequency of assessment of the patient's weight<br>• Addition of a benefit-risk assessment<br>• Clarification of Exclusion criterion 21: Previous use of an investigational drug |
| 27 February 2020 | • Extension of the maximum treatment period from 28 days to 42 days (i. e., the opening of Cohort 2)<br>• Associated changes to the Inclusion and Exclusion criteria in regard to patients with osteomyelitis, epidural or cerebral abscess, or known or suspected left-sided infective endocarditis.<br>• Clarification that creatinine clearance assessment was not required for dialysis patients |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported