



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
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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
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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 ($\text{CLCR} \geq 50 \text{ mL/min}$), 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 ($\text{CLCR} < 50 \text{ mL/min}$).

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

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

End points

End points reporting groups

Reporting group title	Ceftobiprole
Reporting group description: Ceftobiprole 500 mg (as 667 mg ceftobiprole medocartil) 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 (\pm 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 (\pm 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
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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
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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 (\pm 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
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End point timeframe:

At PTE visit on Day 70 (\pm 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 (\pm 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:	
Comparison of all-cause mortality rates in the mITT population	
End point type	Secondary
End point timeframe:	
At PTE visit on Day 70 (\pm 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 (\pm 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 (\pm 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. discontin.	18	18		
Study drug-related AEs leading to treat. discontin.	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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Daptomycin
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Reporting group description:

Daptomycin

Reporting group title	Ceftobiprole
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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			

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	<ul style="list-style-type: none">• Reduction of the number of required signs and symptoms• Vital signs and laboratory tests obtained prior to informed consent• Addition of ± 3 days to visits on Day 35 and Day 42• Discontinuation of treatment if <i>S. aureus</i> has reduced susceptibility• Restriction of Gram-negative treatment blinding to active treatment• Continuation of contraception until 7 days after last dose• Change in frequency of assessment of the patient's weight• Addition of a benefit-risk assessment• Clarification of Exclusion criterion 21: Previous use of an investigational drug
27 February 2020	<ul style="list-style-type: none">• Extension of the maximum treatment period from 28 days to 42 days (i. e., the opening of Cohort 2)• 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.• 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