



Clinical trial results:

A randomized, double-blind, multicenter study to establish the safety and efficacy of ceftobiprole medocartil compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections

Summary

EudraCT number	2017-001605-32
Trial protocol	HU BG
Global end of trial date	22 April 2019

Results information

Result version number	v1
This version publication date	02 May 2020
First version publication date	02 May 2020
Summary attachment (see zip file)	BPR-CS-008 Protocol Synopsis (BPR-CS-008 Protocol Synopsis 6.0.pdf)

Trial information

Trial identification

Sponsor protocol code	BPR-CS-008
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03137173
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Basilea Pharmaceutica International Ltd
Sponsor organisation address	Grenzacherstrasse 487, Basel, Switzerland, 4005
Public contact	Kamal Hamed, Basilea Pharmaceutica International Ltd, Kamal.Hamed@basilea.com
Scientific contact	Kamal Hamed, Basilea Pharmaceutica International Ltd, Kamal.Hamed@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	06 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2019
Global end of trial reached?	Yes
Global end of trial date	22 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary and the main secondary objectives were region-specific. For submission to the U.S. Food and Drug Administration (FDA), the primary objective was to demonstrate the non-inferiority of ceftobiprole to vancomycin plus aztreonam in patients with acute bacterial skin and skin structure infections (ABSSSIs) with respect to early clinical response based on percent reduction in lesion size at 48–72 hours after first treatment in the Intent-to-Treat (ITT) population. For submission to the European Medicines Agency (EMA), the primary objective was to demonstrate the non-inferiority of ceftobiprole to vancomycin plus aztreonam in patients with ABSSSIs, with respect to investigator-assessed clinical success at the test-of-cure (TOC) visit 15–22 days after randomization, in the co-primary ITT and Clinically Evaluable (CE) populations. This is in accordance with the guidelines from these two regulatory authorities (FDA 2013 and EMA 2014).

Protection of trial subjects:

No additional pain or distress was caused by the use of the investigational product.

Background therapy:

None

Evidence for comparator:

The study was designed in accordance with the current U.S. FDA "Guidance for Industry, Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment" (October 2013), and the EMA "Addendum to the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections" (May 2014). The active comparator treatment, vancomycin, is the standard treatment for ABSSSI, recognized as such in current guidelines.

Actual start date of recruitment	19 February 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	Bulgaria: 96
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	United States: 418
Country: Number of subjects enrolled	Ukraine: 162
Worldwide total number of subjects	679
EEA total number of subjects	99

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)	586
From 65 to 84 years	89
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 19 February 2018 and ended on 22 February 2019. Patients were recruited in the following countries: Bulgaria, Hungary, Ukraine, and USA. Only male or female patients aged ≥ 18 years could be enrolled.

Pre-assignment

Screening details:

Patients with an ABSSSI who received any systemic antibacterial treatment within 14 days, or topical antibacterial administration on the primary lesion within 96 hours, before first infusion of study drug were ineligible for enrollment in the study.

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:

The only unblinded site team member was the unblinded pharmacist. The unblinded pharmacist provided blinded and properly-labeled study medication, and was the only team member with access to treatment codes via the IWRS. Blinded treatment labels were affixed on the prepared infusion bags and corresponding documents. All pharmacy documents which could lead to potential unblinding remained secured.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ceftobiprole ITT population

Arm description:

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, an advanced cephalosporin that has been developed for intravenous (IV) administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens, including those that have developed various forms of antibacterial resistance. The recommended dose of ceftobiprole is 500 mg administered as a 2-hour IV infusion every 8 hours.

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

Dosage and administration details:

Ceftobiprole 500 mg was to be administered as a 2-hour IV infusion every 8 hours (with dose adjustment for renal impairment). The treatment duration was for a minimum of 5 days and a maximum of 10 days. Treatment could be extended up to 14 days if in the investigator's opinion this was required, and the extension was approved by the sponsor's medical monitor.

Arm title	Vancomycin+Aztreonam ITT population
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Arm description:

Vancomycin is an antibacterial agent that inhibits bacterial cell wall synthesis and alters cell-membrane permeability and RNA synthesis, with a mean half-life of 4–6 hours. The usual daily IV dose of vancomycin is 2000 mg, administered either as 500 mg every 6 hours or 1000 mg every 12 hours. Patient factors, such as age, obesity, or renal function, may require modification of the daily IV dose. Aztreonam is an antibacterial agent that acts by inhibition of bacterial cell wall synthesis. It confers selective activity against Gram-negative aerobic bacteria, and is not efficacious against Gram-positive bacteria. Aztreonam has been used in previous Phase 3 ABSSSI studies with a dose regimen of 1000 mg every 12 hours in combination with vancomycin, which lacks efficacy against Gram-negative bacteria. The requirement for aztreonam therapy was to be reassessed at the 72-hour study visit.

Arm type	Active comparator
Investigational medicinal product name	Vancomycin 1000 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dosage regimen used for vancomycin at the study site for all patients was agreed by the investigator and the unblinded pharmacist (or delegate) before randomization. Vancomycin dose adjustment for morbidly obese and hypermetabolic patients was according to local standard of care. Vancomycin 1000 mg (or 15 mg/kg) was to be administered as a 2-hour infusion every 12 hours (with dose adjustment for renal impairment). When locally available, vancomycin trough testing (VTT) might be used by the unblinded pharmacist or delegate to adjust the vancomycin dosing. The treatment duration was for a minimum of 5 days and a maximum of 10 days. Treatment could be extended up to 14 days if in the investigator's opinion this was required, and the extension was approved by the sponsor's medical monitor.

Investigational medicinal product name	Aztreonam 1000 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aztreonam 1000 mg was to be administered as a 0.5-hour IV infusion every 12 hours. If CLCR was < 30 mL/min (i.e., severe renal impairment), the aztreonam dosage regimen was to be adjusted. The requirement to continue aztreonam therapy beyond Day 3 was to be reassessed at the 72-hour study visit.

Number of subjects in period 1	Ceftobiprole ITT population	Vancomycin+Aztreonam ITT population
Started	335	344
Completed	309	308
Not completed	26	36
Adverse event, serious fatal	1	3
Consent withdrawn by subject	8	13
Physician decision	1	-
Other reasons	3	2
Lost to follow-up	13	18

Baseline characteristics

Reporting groups

Reporting group title	Ceftobiprole ITT population
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Reporting group description:

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, an advanced cephalosporin that has been developed for intravenous (IV) administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens, including those that have developed various forms of antibacterial resistance. The recommended dose of ceftobiprole is 500 mg administered as a 2-hour IV infusion every 8 hours.

Reporting group title	Vancomycin+Aztreonam ITT population
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Reporting group description:

Vancomycin is an antibacterial agent that inhibits bacterial cell wall synthesis and alters cell-membrane permeability and RNA synthesis, with a mean half-life of 4–6 hours. The usual daily IV dose of vancomycin is 2000 mg, administered either as 500 mg every 6 hours or 1000 mg every 12 hours. Patient factors, such as age, obesity, or renal function, may require modification of the daily IV dose. Aztreonam is an antibacterial agent that acts by inhibition of bacterial cell wall synthesis. It confers selective activity against Gram-negative aerobic bacteria, and is not efficacious against Gram-positive bacteria. Aztreonam has been used in previous Phase 3 ABSSSI studies with a dose regimen of 1000 mg every 12 hours in combination with vancomycin, which lacks efficacy against Gram-negative bacteria. The requirement for aztreonam therapy was to be reassessed at the 72-hour study visit.

Reporting group values	Ceftobiprole ITT population	Vancomycin+Aztreonam ITT population	Total
Number of subjects	335	344	679
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)	294	292	586
From 65-84 years	39	50	89
85 years and over	2	2	4
Age continuous			
Units: years			
arithmetic mean	49	49	
full range (min-max)	18 to 89	20 to 87	-
Gender categorical			
Units: Subjects			
Female	137	143	280
Male	198	201	399
Geographical region			
Subject enrolled in North America and Europe			
Units: Subjects			
North America	203	215	418
Europe	132	129	261
Type of ABSSSI			
Type of ABSSSI at the time of ICF signature			

Units: Subjects			
Cellulitis/erysipelas	112	111	223
Major cutaneous abscess	96	93	189
Wound infection	127	140	267
Race and Ethnicity			
Units: Subjects			
White	318	330	648
Black or African American	7	8	15
Asian	0	1	1
American Indian or Alaska Native	4	3	7
Native Hawaiian or other Pacific Islander	1	0	1
Other	5	2	7

End points

End points reporting groups

Reporting group title	Ceftobiprole ITT population
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Reporting group description:

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, an advanced cephalosporin that has been developed for intravenous (IV) administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens, including those that have developed various forms of antibacterial resistance. The recommended dose of ceftobiprole is 500 mg administered as a 2-hour IV infusion every 8 hours.

Reporting group title	Vancomycin+Aztreonam ITT population
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Reporting group description:

Vancomycin is an antibacterial agent that inhibits bacterial cell wall synthesis and alters cell-membrane permeability and RNA synthesis, with a mean half-life of 4–6 hours. The usual daily IV dose of vancomycin is 2000 mg, administered either as 500 mg every 6 hours or 1000 mg every 12 hours. Patient factors, such as age, obesity, or renal function, may require modification of the daily IV dose. Aztreonam is an antibacterial agent that acts by inhibition of bacterial cell wall synthesis. It confers selective activity against Gram-negative aerobic bacteria, and is not efficacious against Gram-positive bacteria. Aztreonam has been used in previous Phase 3 ABSSSI studies with a dose regimen of 1000 mg every 12 hours in combination with vancomycin, which lacks efficacy against Gram-negative bacteria. The requirement for aztreonam therapy was to be reassessed at the 72-hour study visit.

Subject analysis set title	Ceftobiprole CE population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The CE population was the subset of patients in the ceftobiprole ITT population who complied with important aspects of the study until TOC visit, i.e., with no major protocol deviations.

Subject analysis set title	Vancomycin+Aztreonam CE population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The CE population was the subset of patients in the Vancomycin+Aztreonam ITT population who complied with important aspects of the study until TOC visit, i.e., with no major protocol deviations.

Primary: Investigator-assessed clinical success at the TOC visit 15–22 days after randomization and at least 5 days after the end of treatment in the ITT population

End point title	Investigator-assessed clinical success at the TOC visit 15–22 days after randomization and at least 5 days after the end of treatment in the ITT population
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End point description:

Clinical success assessed by the investigator used a four-point scale relative to the baseline assessment: cured, improved, stable, or worsened. If worsened, (e.g., bacteremia, osteomyelitis, amputation), signs and symptoms were documented as adverse events (AEs). Clinical success was defined as complete (cured) or nearly complete (improved) resolution of baseline signs and symptoms of the primary infection, such that no further antibacterial treatment was needed.

End point type	Primary
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End point timeframe:

15–22 days after randomization

End point values	Ceftobiprole ITT population	Vancomycin+Aztreonam ITT population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	344		
Units: Number of patients	302	306		

Statistical analyses

Statistical analysis title	Non-inferiority test in the ITT population
Statistical analysis description:	
Non-inferiority was assessed by the two-sided 95% confidence interval (CI) of the between-group difference (ceftobiprole minus vancomycin+aztreonam) using a 10% non-inferiority margin in the ITT population. Difference was computed using the Cochran-Mantel-Haenszel (CMH) weights method, adjusted for geographical region and actual type of ABSSSI.	
Comparison groups	Ceftobiprole ITT population v Vancomycin+Aztreonam ITT population
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	5.6

Primary: Investigator-assessed clinical success at the TOC visit 15–22 days after randomization and at least 5 days after the end of treatment in the CE population

End point title	Investigator-assessed clinical success at the TOC visit 15–22 days after randomization and at least 5 days after the end of treatment in the CE population
End point description:	
Clinical success assessed by the investigator used a four-point scale relative to the baseline assessment: cured, improved, stable, or worsened. If worsened, (e.g., bacteremia, osteomyelitis, amputation), signs and symptoms were documented as AEs. Clinical success was defined as complete (cured) or nearly complete (improved) resolution of baseline signs and symptoms of the primary infection, such that no further antibacterial treatment was needed.	
End point type	Primary
End point timeframe:	
15–22 days after randomization	

End point values	Ceftobiprole CE population	Vancomycin+Aztreonam CE population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	283	293		
Units: Number of patients	277	279		

Statistical analyses

Statistical analysis title	Non-inferiority test in the CE population
Statistical analysis description:	
Non-inferiority was assessed by the two-sided 95% CI of the between-group difference (ceftobiprole minus vancomycin+aztreonam) using a 10% non-inferiority margin in the CE population. Difference was computed using the CMH weights method, adjusted for geographical region and actual type of ABSSSI.	
Comparison groups	Ceftobiprole CE population v Vancomycin+Aztreonam CE population
Number of subjects included in analysis	576
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	5.6

Secondary: Early clinical response 48–72 hours after start of treatment in the ITT population

End point title	Early clinical response 48–72 hours after start of treatment in the ITT population
End point description:	
The secondary endpoint was the early clinical response in the ITT population, based on the percent reduction in lesion size at 48– to 72 hours compared to baseline, measured in patients who did not receive rescue therapy and were alive.	
Early clinical response 48–72 hours after start of treatment met all of the following criteria:	
1. $\geq 20\%$ reduction from baseline in the area of the primary lesion	
2. Survival for ≥ 72 hours from the time of administration of the first dose of study drug	
3. No use of concomitant systemic antibacterial treatments, or topical antibacterial administration on the primary lesion before or on the latest lesion measurement done within 48–72 hours after the first dose of study drug	
4. No additional unplanned surgical procedure for the ABSSSI after start of therapy and before or on the day of latest lesion measurement done within 48–72 hours after the first dose of study drug.	
End point type	Secondary
End point timeframe:	
48–72 hours after start of treatment	

End point values	Ceftobiprole ITT population	Vancomycin+A ztreonam ITT population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	344		
Units: Number of patients	306	303		

Statistical analyses

Statistical analysis title	Non-inferiority test in the ITT population
Statistical analysis description:	
Non-inferiority was assessed by the two-sided 95% CI of the between-group difference (ceftobiprole minus vancomycin+aztreonam) using a 10% non-inferiority margin in the ITT population. Difference was computed using the CMH weights method, adjusted for geographical region and actual type of ABSSSI.	
Comparison groups	Ceftobiprole ITT population v Vancomycin+Aztreonam ITT population
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	7.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Relevant change / worsening of a patient's status after informed consent (before start of first study-drug infusion) was recorded in medical history. From start of first dosing to and including the last follow-up visit, these data were recorded as AEs.

Adverse event reporting additional description:

Once an AE was detected, it was to be proactively followed up at each visit (or more frequently if necessary) for any changes in severity, relationship to the study drug, interventions required for treatment, and the event's outcome. Serious adverse events (SAEs) were to be additionally reported and recorded on SAE report forms.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Ceftobiprole (Safety population)
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Reporting group description:

Safety population: all randomized patients who received at least one dose of study drug.

Reporting group title	Vancomycin+Aztreonam (Safety population)
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Reporting group description:

Safety population: all randomized patients who received at least one dose of study drug.

Serious adverse events	Ceftobiprole (Safety population)	Vancomycin+Aztreonam (Safety population)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 334 (1.80%)	12 / 342 (3.51%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	1	2	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 334 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 334 (0.30%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac arrest			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Multiple allergies			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 334 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 334 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 334 (0.30%)	0 / 342 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 334 (0.00%)	2 / 342 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			

subjects affected / exposed	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 342 (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	0 / 334 (0.00%)	1 / 342 (0.29%)	
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	0 / 334 (0.00%)	1 / 342 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin bacterial infection			
subjects affected / exposed	1 / 334 (0.30%)	3 / 342 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ceftobiprole (Safety population)	Vancomycin+Aztreonam (Safety population)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 334 (18.86%)	47 / 342 (13.74%)	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 334 (5.69%)	24 / 342 (7.02%)	
occurrences (all)	21	29	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	21 / 334 (6.29%)	16 / 342 (4.68%)	
occurrences (all)	22	16	
Nausea			

subjects affected / exposed	36 / 334 (10.78%)	20 / 342 (5.85%)	
occurrences (all)	37	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2018	<ol style="list-style-type: none">1. To comply with Competent Authority recommendation, the temperature ranges for the definition of fever was specified in inclusion criteria according to the methods of measurement (inclusion criterion 3b).2. During medical monitoring, it was noted that a high proportion of patients enrolled in the study were illicit drug users. The sponsor therefore limited the further enrollment of illicit drug users in the study to better support generalisation of the study results in the context of clinical practice. In addition, a subgroup analysis was added to include illicit drug use as a pre-specified subgroup. The following exclusion criterion was added: "Patients with illicit drug use within 12 months of screening, including heroin, other opioids (unless prescribed for medical reasons unrelated to heroin substitution), cocaine / crack cocaine, and amphetamine/methamphetamine. Exception: Cannabis use."3. Delafloxacin and meropenem/vaborbactam were added to the protocol list of antibiotics meeting the criterion of a half-life \leq 12 hours.4. Clarification was added of the circumstances in which the re-administration of aztreonam was permitted at any point during the study treatment period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported