Clinical trial results:
A multicentre, randomized, investigator-blind, active-controlled study to evaluate the safety, tolerability, pharmacokinetics and efficacy of ceftobiprole versus intravenous standard-of-care cephalosporin treatment with or without vancomycin in paediatric patients aged from 3 months to less than 18 years with hospital-acquired pneumonia or community-acquired pneumonia requiring hospitalisation

Summary

EudraCT number	2013-004615-45
Trial protocol	HU BG Outside EU/EEA
Global end of trial date	16 March 2020

Results information

Result version number	v1
This version publication date	06 September 2020
First version publication date	06 September 2020
Summary attachment (see zip file)	BPR-PIP-002 Protocol Synopsis (BPR-PIP-002 Protocol Synopsis Version 3.0_for publishing in EudraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	BPR-PIP-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03439124
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Basilea Pharmaceutica International Ltd
Sponsor organisation address	Grenzacherstrasse 487, Basel, Switzerland, 4058
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000205-PIP02-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2020
Global end of trial reached?	Yes
Global end of trial date	16 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterise the safety profile of ceftobiprole in paediatric patients with either hospital-acquired pneumonia (HAP) or community-acquired pneumonia (CAP) requiring hospitalisation, and requiring intravenous (IV) antibiotic therapy.

Protection of trial subjects:

Throughout the study, the paediatric study participants were observed carefully for any potential side effects. No additional pain or distress was caused by the use of the investigational product.

Background therapy:

None

Evidence for comparator:

The active comparator treatments, ceftriaxone for CAP and ceftazidime for HAP, are standard-of-care IV antibiotics. In addition, vancomycin was added when methicillin-resistant Staphylococcus aureus (MRSA) was suspected or confirmed.

Actual start date of recruitment	27 November 2017
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: 38
Country: Number of subjects enrolled	Hungary: 57
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Georgia: 39
Worldwide total number of subjects	138
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)	14
Children (2-11 years)	95
Adolescents (12-17 years)	29
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 27 November 2017 and ended on 2 February 2020. Patients were recruited in the following countries: Bulgaria, Georgia, Hungary, and Romania. Only paediatric patients aged from 3 months to < 18 years could be enrolled.

Pre-assignment

Screening details:

Paediatric patients with either HAP (pneumonia occurring after ≥ 48 hours of hospitalisation) or CAP requiring hospitalization, and requiring administration of IV antibiotic therapy, were eligible.

Period 1

Period 1 title	ITT/Safety population (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

There was at least one blinded investigator at each center who did not know the patient's assigned treatment. This blinded observer conducted the clinical outcome assessments, as well as assessments of the criteria for switching to oral antibiotic therapy. Such assessments were made on the patient ward when no study drugs were being administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ceftobiprole ITT/Safety population

Arm description:

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, an advanced-generation cephalosporin developed for IV administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens.

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

Dosage and administration details:

Ceftobiprole medocaril was to be administered at age-adjusted doses (10, 15 or 20 mg/kg) and infusion durations (2 or 4 hours) every 8 hours. The maximum dose, regardless of body weight, was 500 mg ceftobiprole every 8 hours (maximum total daily dose of 1500 mg ceftobiprole).
After a minimum of 3 days of IV treatment, patients with sufficient improvement in disease signs and symptoms could be switched to an age-appropriate oral antibiotic to complete a total minimum of 7 days and a total maximum of 14 days' antibiotic treatment.

Arm title	IV standard-of-care cephalosporin ITT/Safety population

Arm description:

Ceftriaxone was used as standard-of-care cephalosporin for the treatment of CAP. It is a third-generation cephalosporin with activity against typical bacterial pathogens of CAP requiring hospitalisation, and is widely used for the treatment of various bacterial infections in neonates, infants, children, and adults.
Ceftazidime was used as standard-of-care cephalosporin for the treatment of HAP. It is also a third-generation cephalosporin, but with broader activity against Gram-negative aerobic bacilli, including Pseudomonas aeruginosa.
Vancomycin is a glycopeptide antibiotic that is active against staphylococci, including MRSA. Patients were to receive vancomycin in addition to the IV standard-of-care cephalosporin when MRSA was suspected or confirmed, or at the discretion of the blinded investigator.

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

Dosage and administration details:

Ceftriaxone was to be administered at 50 to 80 mg/kg IV as a single daily dose, up to a maximum dose of 2 g/day. The actual dose of ceftriaxone within this dose range was to be determined by the blinded investigator prior to first study drug administration and was not to be modified during subsequent study days.
After a minimum of 3 days of IV treatment, patients with sufficient improvement in disease signs and symptoms could be switched to an age-appropriate oral antibiotic to complete a total minimum of 7 days and a total maximum of 14 days' antibiotic treatment.
At the discretion of the blinded investigator, patients were to receive vancomycin at a dose of 10 to 15 mg/kg IV every 6 hours, up to a maximum dose of 2 g/day, in addition to the IV standard-of-care cephalosporin when MRSA was suspected or confirmed.

Investigational medicinal product name	Ceftazidime
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ceftazidime was to be administered at 50 mg/kg IV every 8 hours, up to a maximum of 6 g/day.
After a minimum of 3 days of IV treatment, patients with sufficient improvement in disease signs and symptoms could be switched to an age-appropriate oral antibiotic to complete a total minimum of 7 days and a total maximum of 14 days' antibiotic treatment.
At the discretion of the blinded investigator, patients were to receive vancomycin at a dose of 10 to 15 mg/kg IV every 6 hours, up to a maximum dose of 2 g/day, in addition to the IV standard-of-care cephalosporin when MRSA was suspected or confirmed.

Investigational medicinal product name	Vancomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vancomycin was to be administered at 10 to 15 mg/kg IV every 6 hours, up to a maximum dose of 2 g/day, in addition to the IV standard-of-care cephalosporin when MRSA was suspected or confirmed, at the discretion of the blinded investigator. Vancomycin serum concentrations were to be monitored in all patients receiving vancomycin and the dosage was to be adjusted by the unblinded investigator as needed to maintain serum concentrations within the therapeutic window.
Vancomycin dosage in patients with impaired renal function was to be modified in accordance with the approved product label.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: In order to avoid excessive total volumes of IV fluid that would be administered to paediatric patients with a double-blind, double-dummy study design, this was an investigator-blind study which allowed for an unbiased assessment of the safety profile and efficacy outcomes of the study treatment.

Number of subjects in period 1	Ceftobiprole ITT/Safety population	IV standard-of-care cephalosporin ITT/Safety population
Started	94	44
Completed	90	44
Not completed	4	0
Adverse event, non-fatal	2	-
Other	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ceftobiprole ITT/Safety population
Reporting group description:	
Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, an advanced-generation cephalosporin developed for IV administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens.	
Reporting group title	IV standard-of-care cephalosporin ITT/Safety population
Reporting group description:	
Ceftriaxone was used as standard-of-care cephalosporin for the treatment of CAP. It is a third-generation cephalosporin with activity against typical bacterial pathogens of CAP requiring hospitalisation, and is widely used for the treatment of various bacterial infections in neonates, infants, children, and adults. Ceftazidime was used as standard-of-care cephalosporin for the treatment of HAP. It is also a third-generation cephalosporin, but with broader activity against Gram-negative aerobic bacilli, including Pseudomonas aeruginosa. Vancomycin is a glycopeptide antibiotic that is active against staphylococci, including MRSA. Patients were to receive vancomycin in addition to the IV standard-of-care cephalosporin when MRSA was suspected or confirmed, or at the discretion of the blinded investigator.	

Reporting group values	Ceftobiprole ITT/Safety population	IV standard-of-care cephalosporin ITT/Safety population	Total
Number of subjects	94	44	138
Age categorical			
Randomisation of trial subjects was stratified by four age groups (3 months to <2 years; 2 years to <6 years; 6 years to <12 years; 12 years to <18 years).			
Units: Subjects			
Patients aged 3 months to <2 years	12	2	14
Patients aged 2 years to <6 years	37	19	56
Patients aged 6 years to <12 years	27	12	39
Patients aged 12 years to <18 years	18	11	29
Age continuous			
Units: years			
arithmetic mean	6.81	6.95	
full range (min-max)	0.6 to 17.0	1.0 to 17.0	-
Gender categorical			
Units: Subjects			
Female	41	23	64
Male	53	21	74
Race			
Units: Subjects			
Black or African American	0	1	1
White	94	43	137
Infection type			
Randomisation of trial subjects was stratified by diagnosis of HAP or CAP.			
Units: Subjects			
HAP	5	3	8
CAP	89	41	130

End points

End points reporting groups

Reporting group title	Ceftobiprole ITT/Safety population

Reporting group description:

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, an advanced-generation cephalosporin developed for IV administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens.

Reporting group title	IV standard-of-care cephalosporin ITT/Safety population

Reporting group description:

Ceftriaxone was used as standard-of-care cephalosporin for the treatment of CAP. It is a third-generation cephalosporin with activity against typical bacterial pathogens of CAP requiring hospitalisation, and is widely used for the treatment of various bacterial infections in neonates, infants, children, and adults.
Ceftazidime was used as standard-of-care cephalosporin for the treatment of HAP. It is also a third-generation cephalosporin, but with broader activity against Gram-negative aerobic bacilli, including Pseudomonas aeruginosa.
Vancomycin is a glycopeptide antibiotic that is active against staphylococci, including MRSA. Patients were to receive vancomycin in addition to the IV standard-of-care cephalosporin when MRSA was suspected or confirmed, or at the discretion of the blinded investigator.

Subject analysis set title	Ceftobiprole ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included are all randomised patients of the study drug group (ceftobiprole).

Subject analysis set title	IV standard-of-care cephalosporin ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included are all randomised patients in the comparator group (IV standard-of-care cephalosporin).

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

Subject analysis set description:

Included are all patients who had a valid clinical outcome assessment at TOC and no major protocol deviations such as non-study antibiotic therapies.

Subject analysis set title	IV standard-of-care cephalosporin CE population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included are all patients who had a valid clinical outcome assessment at TOC and no major protocol deviations such as non-study antibiotic therapies.

Primary: Adverse events

End point title	Adverse events[1]

End point description:

Reported are adverse events (AEs) during the first 3 days of IV therapy and while patients were on IV therapy irrespective of when they switched to oral antibiotic treatment.

End point type	Primary

End point timeframe:

Analysis of AEs assessed during the first 3 days of IV therapy and while on IV

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary objective of this study was to evaluate the safety and tolerability of ceftobiprole in children and the study was not powered for formal statistical analysis.

End point values	Ceftobiprole ITT/Safety population	IV standard-of-care cephalosporin ITT/Safety population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	44		
Units: Number of patients				
Any TEAE (first 3 days of IV therapy)	11	5		
Serious TEAE (first 3 days of IV therapy)	1	0		
TEAE leading to death (first 3 days of IV therapy)	0	0		
Any TEAE (while on IV therapy)	19	8		
Serious TEAE (while on IV therapy)	2	0		
TEAE leading to death (while on IV therapy)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure rate ITT population

End point title	Clinical cure rate ITT population

End point description:

Comparison of clinical cure rates in the ITT population between ceftobiprole and the comparator at the TOC visit.

End point type	Secondary

End point timeframe:

At the TOC visit

End point values	Ceftobiprole ITT population	IV standard-of-care cephalosporin ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	44		
Units: Number of patients	85	43		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure rate CE population

End point title	Clinical cure rate CE population

End point description:

Comparison of clinical cure rates in the CE population between ceftobiprole and the comparator at the TOC visit.

End point type	Secondary

End point timeframe:

At the TOC visit

End point values	Ceftobiprole CE population	IV standard-of-care cephalosporin CE population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	41		
Units: Number of patients	80	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Early clinical response rate ITT population

End point title	Early clinical response rate ITT population

End point description:

Comparison of early clinical response rates in the ITT population between ceftobiprole and the comparator at Day 4.

End point type	Secondary

End point timeframe:

At Day 4

End point values	Ceftobiprole ITT population	IV standard-of-care cephalosporin ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	44		
Units: Number of patients	90	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Early clinical response rate CE population

End point title	Early clinical response rate CE population

End point description:

Comparison of early clinical response rates in the CE population between ceftobiprole and the comparator at Day 4.

End point type	Secondary

End point timeframe:
At Day 4

End point values	Ceftobiprole CE population	IV standard-of-care cephalosporin CE population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	41		
Units: Number of patients	84	39		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Relevant 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, such worsening was recorded as an AE.

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Ceftobiprole overall study

Reporting group description:

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, an advanced-generation cephalosporin that has been developed for IV administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both gram-positive and gram-negative pathogens.

Reporting group title	IV standard-of-care cephalosporin overall study

Reporting group description: -

Serious adverse events	Ceftobiprole overall study	IV standard-of-care cephalosporin overall study	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 94 (7.45%)	2 / 44 (4.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Seizure like phenomena			
subjects affected / exposed	0 / 94 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 94 (1.06%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	1 / 94 (1.06%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 94 (1.06%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 94 (1.06%)	0 / 44 (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			
Pneumonia			
subjects affected / exposed	3 / 94 (3.19%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis streptococcal			
subjects affected / exposed	1 / 94 (1.06%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ceftobiprole overall study	IV standard-of-care cephalosporin overall study	
Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 94 (8.51%)	5 / 44 (11.36%)	
Gastrointestinal disorders Vomiting subjects affected / exposed	6 / 94 (6.38%)	1 / 44 (2.27%)	
occurrences (all)	6	1	
Diarrhoea subjects affected / exposed	2 / 94 (2.13%)	4 / 44 (9.09%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2018	1. Inclusion criteria 3 (Diagnosis of either HAP (pneumonia occurring after ≥ 48 hours of hospitalisation) or CAP requiring hospitalisation and administration of IV antibiotic therapy) and 4 (New or progressive imaging findings consistent with bacterial pneumonia) were clarified. 2. Exclusion criterion 9 was amended to clarify that there was no requirement to conduct a rapid diagnostic test for influenza or respiratory syncytial virus. 3. Amendments were made to Section 5.6.2 Safety laboratory tests: (a) it was added that creatinine clearance was to be estimated throughout the study using the Schwartz Estimate and (b) an inadvertent omission of aspartate aminotransferase (AST) from blood chemistry parameters to be analyzed in safety laboratory tests was corrected. 4. The sponsor's pharmacovigilance service provider changed. The Safety contact was changed from ICON Clinical Research Limited to PrimeVigilance Limited.
29 November 2018	1. The sample size was reduced from 250 patients to 138 patients, in accordance with modification of the Paediatric Investigation Plan (PIP) as decided by the EU Paediatric Committee (PDCO). 2. The estimation of the > 95% probability of observing at least one AE type was adjusted consistent with the reduction in sample size (see above). 3. An exception was added to exclusion criterion 13 (use of systemic antimicrobial therapy for more than 24 hours in the 48 hours before randomisation for the current episode of pneumonia) to remove an inconsistency with inclusion criterion 3 for CAP patients with failure to clinically improve on initial antibiotic therapy for at least 48 hours and a need for antibiotic treatment. The interim analysis was clarified with regard to blinding and the required number of patients for the interim analysis of safety data was reduced consistent with the reduction in sample size (see above).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported