Clinical trial results:
An open-label study to evaluate the single-dose pharmacokinetics and safety of ceftobiprole in neonate and infant subjects aged up to 3 months undergoing treatment with systemic antibiotics

Summary

EudraCT number	2013-004614-18
Trial protocol	BE DE LT PL LV Outside EU/EEA
Global end of trial date	07 July 2020

Results information

Result version number	v2 (current)
This version publication date	01 June 2023
First version publication date	27 December 2020
Version creation reason	• New data added to full data set Update of contact information

Trial information

Trial identification

Sponsor protocol code	BPR-PIP-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02527681
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Basilea Pharmaceutica International Ltd.
Sponsor organisation address	Grenzacherstrasse 487, Basel, Switzerland, 4058
Public contact	Chief Medical Officer, Marc Engelhardt, Basilea Pharmaceutica International Ltd., +41 797010551, marc.engelhardt@basilea.com
Scientific contact	Chief Medical Officer, Marc Engelhardt, Basilea Pharmaceutica International Ltd., +41 797010551, marc.engelhardt@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	15 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2020
Global end of trial reached?	Yes
Global end of trial date	07 July 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to characterise the pharmacokinetics of a single dose of ceftobiprole in neonates and infants aged ≤ 3 months.

Protection of trial subjects:

As eligible subjects were already receiving standard-of-care intravenous antibiotic treatment, the administration of ceftobiprole did not impose substantial additional discomfort or risk. Laboratory tests required for screening, but which had been performed within the 48 hours prior to ceftobiprole dosing, were not to be repeated, regardless of whether they had been performed before or after signing of the ICF.

Background therapy:

Standard-of-care antibiotic

Evidence for comparator:

Not applicable

Actual start date of recruitment	22 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	15
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	9
Infants and toddlers (28 days-23 months)	6
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 22-Nov-2016 and ended on 18-Feb-2020. 45 neonate or infant subjects, stratified for gestational and postnatal age, were planned to be enrolled in three sequential cohorts. After agreement with the EMA Paediatric Committee, the study was terminated after enrolment of the full-term cohort. No pre-term subjects were enrolled.

Pre-assignment

Screening details:

Subjects with documented or presumed bacterial infection receiving standard-of-care antibiotic treatment were screened.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ceftobiprole ITT/Safety population

Arm description:

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, an advanced-generation cephalosporin developed for intravenous 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 infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ceftobiprole medocaril was administered as a single intravenous infusion, with a bodyweight-adjusted volume, at a constant rate over 4 hours. The ceftobiprole dose was 7.5 mg/kg, which corresponds to 10.0 mg ceftobiprole medocaril.

Number of subjects in period 1	Ceftobiprole ITT/Safety population
Started	15
Completed	15

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	9	9	
Infants and toddlers (28 days-23 months)	6	6	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: days			
median	13.0		
inter-quartile range (Q1-Q3)	8.0 to 43.0	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	10	10	
Race Units: Subjects			
White	13	13	
Black or African American	1	1	
Native Hawaiian or Other Pacific Islander	1	1	

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 intravenous administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens.

Subject analysis set title	Pharmacokinetics analysis population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetics analysis population comprised all subjects who received study drug and had adequate samples for determination of time-plasma concentration profiles of ceftobiprole.

Primary: Cmax

End point title	Cmax[1]

End point description:

The maximum observed plasma concentration (Cmax)

End point type	Primary

End point timeframe:

Blood samples for PK analysis were obtained pre-dose, and at 2, 4, 6, 8, and 12 hours after the start of dosing.

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: In line with the Paediatric Investigation Plan (PIP) issued by the EMA Paediatric Committee, descriptive statistics have been agreed and is appropriate for this clinical study endpoint

End point values	Pharmacokinetics analysis population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: µg/mL				
median (full range (min-max))	11.2 (8.68 to 32.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Tmax

End point title	Tmax[2]

End point description:

The time of maximum observed plasma concentration (Tmax)

End point type	Primary

End point timeframe:

Blood samples for PK analysis were obtained pre-dose, and at 2, 4, 6, 8, and 12 hours after the start of dosing.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In line with the Paediatric Investigation Plan (PIP) issued by the EMA Paediatric Committee, descriptive statistics have been agreed and is appropriate for this clinical study endpoint

End point values	Pharmacokinetics analysis population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
median (full range (min-max))	4.00 (4.00 to 4.00)			

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-last

End point title	AUC0-last[3]

End point description:

The area under the plasma concentration-time curve from time zero to the time of the last measurable concentration (AUC0-last)

End point type	Primary

End point timeframe:

Blood samples for PK analysis were obtained pre-dose, and at 2, 4, 6, 8, and 12 hours after the start of dosing.

Notes:

[3] - 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: In line with the Paediatric Investigation Plan (PIP) issued by the EMA Paediatric Committee, descriptive statistics have been agreed and is appropriate for this clinical study endpoint

End point values	Pharmacokinetics analysis population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: µg•hours/mL				
median (full range (min-max))	60.6 (49.1 to 126.0)			

Statistical analyses

No statistical analyses for this end point

Primary: T>MIC of 4 mg/L

End point title	T>MIC of 4 mg/L[4]

End point description:

The duration of time after dose for which free-drug concentrations remained above a value of 4 mg/L

(T>MIC of 4 mg/L)

End point type	Primary

End point timeframe:

Blood samples for PK analysis were obtained pre-dose, and at 2, 4, 6, 8, and 12 hours after the start of dosing.

Notes:

[4] - 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: In line with the Paediatric Investigation Plan (PIP) issued by the EMA Paediatric Committee, descriptive statistics have been agreed and is appropriate for this clinical study endpoint

End point values	Pharmacokinetics analysis population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
median (full range (min-max))	5.40 (3.77 to 8.13)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After start of study drug administration through the follow-up visit at study Day 7±3, relevant worsening of a patient's status was to be recorded as an adverse event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

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 intravenous administration. Ceftobiprole is characterised by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens.

Serious adverse events	Ceftobiprole ITT/Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diaphragmatic hernia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ceftobiprole ITT/Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)		

Skin and subcutaneous tissue disorders Dermatitis diaper subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all)	 2 / 15 (13.33%) 2 1 / 15 (6.67%) 1		
Psychiatric disorders Drug Dependence subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2018	Administrative change: new pharmacovigilance service provider.
21 March 2019	Reduction in the number of laboratory blood tests at screening and at the follow-up evaluation. Extension of the window from 24 to 48 hours in which laboratory results available as standard of care could be used for screening.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported