



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 | <ul style="list-style-type: none">• New data added to full data setUpdate 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) | EMA-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