



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) | 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 | 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 | <ol style="list-style-type: none">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 | <ol style="list-style-type: none">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. <p>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).</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported