Protocol synopsis

TITLE	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
SPONSOR	Basilea Pharmaceutica International Ltd ('Basilea')
STUDY PHASE	3
INDICATIONS	Treatment of hospital-acquired pneumonia (HAP) excluding ventilator-associated pneumonia (VAP), and community-acquired pneumonia (CAP).
OBJECTIVES	**Primary objective** To characterise the safety profile of ceftobiprole in paediatric patients with HAP or CAP requiring hospitalisation and intravenous (IV) antibiotic therapy. **Secondary objectives** In paediatric patients with HAP or CAP requiring hospitalisation: • To compare the clinical cure rate and microbiological eradication rate at the test-of-cure (TOC) visit between ceftobiprole and IV standard-of-care cephalosporin treatment (± vancomycin) • To compare the clinical and microbiological relapse rates at the last follow-up (LFU) visit between ceftobiprole and IV standard-of-care cephalosporin treatment (± vancomycin) • To characterise other efficacy measures of ceftobiprole (e.g., improvement in signs and symptoms of pneumonia, length of hospital stay) • To assess the pharmacokinetics (PK) of ceftobiprole
STUDY DESIGN	Randomized, investigator-blind, active-comparator, multiple-fixed dose, multicentre study
PLANNED NUMBER OF PARTICIPANTS	138 patients are planned to be randomized 2:1 to ceftobiprole or standard-of-care comparator treatment. It is estimated that at least 125 of these patients will be evaluable, comprising a minimum of 50 patients for each of the age categories < 6 years and ≥ 6 years. There is no requirement for a minimum number of patients with each infection type (HAP or CAP).
NUMBER OF CENTRES/ LOCATIONS	Approximately 20 European centres; additional centres both within and outside Europe may be considered.

INCLUSION CRITERIA

Patients meeting all of the following at Screening:

1. Male or female aged 3 months to < 18 years
2. Body weight of at least 5 kg
3. Diagnosis of either HAP (pneumonia occurring after ≥48 hours of hospitalisation) or CAP requiring hospitalisation and administration of IV antibiotic therapy, characterised by:
   - Fever (> 38.5 °C) or hypothermia (< 35 °C), and
   - Leucocytosis or leucopenia (relevant to patient age and institutional normal ranges), and
   - At least two of the following signs or symptoms: cough, lower respiratory tract secretions, auscultatory findings of pneumonia, dyspnea/tachypnea, increased work of breathing (retractions, nasal flaring, or grunting), hypoxaemia/oxygen saturation < 92% (on room air)

   Patients with CAP must present with at least one of the following conditions:
   - Admission to an intensive care unit, intermediate care unit, or a unit with the ability to provide constant and close monitoring and care
   - Suspected infection with multi-drug resistant pneumococci or methicillin-resistant *Staphylococcus aureus* (MRSA)
   - History of absent or incomplete pneumococcal vaccination (did not receive all vaccinations as per schedule)
   - Recent clinical diagnosis of influenza with exacerbation of fever and respiratory symptoms after initial improvement in the symptoms of acute influenza
   - Failure to clinically improve on initial antibiotic therapy for at least 48 hours and need for antibiotic treatment change
   - Oxygen saturation on room air ≤ 90%
4. New or progressive imaging findings consistent with bacterial pneumonia (e.g., X-ray, ultrasound, or computer tomography)
5. Requirement for IV antibacterial treatment for pneumonia
6. Sufficient vascular access to receive IV study drug
7. Informed consent from the parent or legally acceptable representative (LAR) to participate in the study, and child's assent as appropriate
8. Female patients who are not pregnant or breast-feeding and meet one of the following conditions:
   - Pre-menarcheal, or
   - A negative serum or urine pregnancy test and willing to use a highly reliable method of contraception during the study until the LFU visit

EXCLUSION CRITERIA	Patients meeting any one of the following at Screening: 1. Known resistance of the causative pathogen to ceftobiprole or IV standard-of-care cephalosporin treatment (± vancomycin) 2. On mechanical ventilation at Screening for more than 48 hours 3. Chest trauma with severe lung contusion or flail chest 4. Acute respiratory distress syndrome 5. Empyema or lung abscess 6. Anatomical bronchial obstruction 7. Documented or suspected active or currently-treated pulmonary tuberculosis 8. Documented or suspected atypical bacterial pneumonia, or viral pneumonia without bacterial superinfection, or need for antibiotic coverage with a macrolide 9. Known positive result from a rapid diagnostic test for influenza or respiratory syncytial virus, unless bacterial pneumonia secondary to viral respiratory illness is suspected based on a clinical history of exacerbation of fever and respiratory symptoms after initial improvement in the symptoms of an acute respiratory infection 10. Documented or suspected pertussis, chemical pneumonitis (e.g., aspiration of gastric contents, inhalation injury), or cystic fibrosis 11. Severe immunodeficiency (HIV infection, or congenital or acquired immunodeficiency syndrome) 12. Significant laboratory abnormalities (based on local laboratory results) including: • Hematocrit < 20% • Absolute neutrophil count < 0.5×10^9/L • Platelet count < 50×10^9/L • Alanine aminotransferase, aspartate aminotransferase, or total bilirubin > 5 × the age-specific upper limit of normal • Creatinine clearance of < 50 mL/min/1.73 m^2, or requirement for any form of renal dialysis therapy 13. Use of systemic antimicrobial therapy for more than 24 hours in the 48 hours before randomization for the current episode of pneumonia Exception: CAP patients with failure to clinically improve on initial antibiotic therapy for at least 48 hours and need for antibiotic treatment change (see Inclusion criterion 3) 14. History of a previous clinically-relevant hypersensitivity or serious adverse reaction to beta-lactam antibiotics or to vancomycin 15. Poorly-controlled seizure disorder (> 1 seizure in the month preceding randomization)
STUDY-DRUG ADMINISTRATION	The study treatments to be administered are: 1. Ceftobiprole medocaril 10 to 20 mg/kg (age-adjusted) IV q8h. 2. Comparator for CAP: ceftriaxone 50 to 80 mg/kg IV as a single daily dose, up to a maximum dose of 2 g/day.

	3. Comparator for HAP: ceftazidime 50 mg/kg IV q8h, up to a maximum of 6 g/day. 4. For patients receiving comparator antibiotics, administration of concomitant vancomycin (10 to 15 mg/kg IV every 6 hours, up to a maximum dose of 2 g/day) is to be added when MRSA is suspected or confirmed.
CONCOMITANT MEDICATION	Patients who require concomitant treatment with a macrolide during the course of the active study-drug treatment period (other than as part of a switch to oral antibiotic treatment as outlined below) should be withdrawn from the study and treated with an appropriate non-study standard-of-care antibiotic regimen. After a minimum of 3 days of study treatments (nine infusions of ceftobiprole or an equivalent number of doses of standard-of-care antibiotic comparator treatment), patients with sufficient improvement in disease signs and symptoms (according to predefined criteria) may be switched to an oral antibiotic to complete a minimum of 7 days antibiotic treatment, at the discretion of the Blinded Investigator. A macrolide may be used for oral switch. The oral antibiotic will be recorded as concomitant medication. In addition, concomitant treatment for suspected infections by *Pseudomonas aeruginosa* may be added at the discretion of the Blinded Investigator. Anti-pseudomonal treatment for both the ceftobiprole and standard-of-care comparator group should comprise gentamicin, amikacin or tobramycin.
BLINDING	Investigator-blind (at least one Blinded Investigator at each centre acts as blinded observer).
TREATMENT DURATION	7–14 days.
MAIN STUDY ENDPOINTS	**Primary endpoint** Analysis of adverse events (AEs) assessed on each of the first 3 days of study-drug treatment, and at the end-of-treatment (EOT), TOC, and LFU visits (Safety population). Other timepoints may also be analysed. **Secondary endpoints** 1. Efficacy: Comparison of clinical cure rates (ITT and CE populations) and microbiological eradication rates (mITT and ME populations) between ceftobiprole and the comparator at the TOC visit; and cure of pneumonia, defined as clinical improvement or lack of progression of X-ray abnormalities, as well as resolution of clinical pneumonia findings, at study Day 4 and the EOT visit (ITT and CE populations). The clinical and microbiological relapse rates at the LFU visit will also be compared (ITT, CE, mITT and ME populations). 2. Pharmacokinetics: Descriptive analysis of ceftobiprole plasma concentration per time point, based on PK sampling in at least 15 patients in each of the two age categories of < 6 years and ≥ 6 years (PK population).

STATISTICAL ANALYSIS	A total of 138 paediatric patients aged 3 months to < 18 years will be enrolled, with a minimum of 50 patients for each of the age categories < 6 years and ≥ 6 years. There is no requirement for a minimum number of patients with each infection type (HAP or CAP). Patients must be diagnosed with HAP or CAP requiring hospitalisation and therapy with IV antibiotics. Randomization will be 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), and by diagnosis of HAP or CAP. No formal hypothesis testing will be performed. Descriptive statistics will be applied to the primary analysis, with frequency tables used to characterise the safety and tolerability profile of ceftobiprole in the safety population. The secondary analysis of clinical cure rates (ITT and CE populations) and microbiological eradication rates (mITT and ME populations) will be compared between ceftobiprole and the standard-of-care comparator. Clinical cure and microbiological eradication rates at TOC will be tabulated for ceftobiprole and comparators and the between-group differences will be displayed along with the respective 95% confidence intervals (CIs). The between-group differences in the rates of patients whose clinical signs and symptoms improved or were cured at Day 4 and at EOT will also be displayed, along with the respective 95% CIs. Signs and symptoms of pneumonia and overall clinical status will be analysed by descriptive statistics. Clinical and microbiological relapse will be assessed at the LFU visit and will be compared between the treatment groups. Descriptive statistics will be applied. Plasma concentrations will be listed and analysed by summary descriptive statistics, including mean, median, standard deviation, coefficient of variation, and range. Analyses will also be presented by age group. **Analysis populations** ***Safety population***: all randomized patients who received at least one dose of study drug, analysed according to the first treatment actually received. ***Intent-to-treat (ITT) population***: all randomized patients, analysed by treatment assigned. ***Clinically evaluable (CE) population***: patients who received at least 3 days (nine infusions) of study drug, had a valid clinical outcome assessment at TOC, no major protocol violations, and no systemic non-study antibiotic therapies. ***Microbiological intent-to-treat (mITT) population***: all patients in the ITT analysis population with a valid pathogen identified at baseline. ***Microbiologically evaluable (ME) population***: all patients in the CE analysis population with a valid pathogen at baseline and a microbiological assessment at TOC. ***Pharmacokinetic (PK) population***: all patients who received at least one dose of ceftobiprole and have at least one plasma-concentration measurement obtained using the appropriate methodology.