NCT03439124

CLINICAL STUDY PROTOCOL

BPR-PIP-002

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

Protocol Number/Version:	BPR-PIP-002 / 3.0
Compound:	Ceftobiprole medocaril
Phase of development:	Phase 3
EudraCT number:	2013-004615-45
Date:	29 November 2018
Project Physician:	[redacted]
Project Statistician:	[redacted]
Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel, Switzerland Tel + 41 61 606 1111

SPONSOR SIGNATURES

Protocol number / Version:	BPR-PIP-002 / 3.0
Study 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
Compound:	Ceftobiprole medocaril
Phase of development:	Phase 3
Date:	29 November 2018
Project Physician:	[redacted]
Project Statistician:	[redacted]
Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel, Switzerland Tel + 41 61 606 1111

Name/Title	Date	Signature
[redacted]	29 Nov 2018	[redacted]
	29 NOV 2018	

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration curve
BLQ	Below limit of quantitation
CAP	Community-acquired pneumonia
CFU	Colony forming unit
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CRF	Case Report Form
EC	Ethics Committee
DSMB	Data and Safety Monitoring Board
EOT	End-of-treatment
ESRD	End-stage renal disease
GCP	Good Clinical Practice
HAP	Hospital-acquired pneumonia
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICU	Intensive care unit
ITT	Intent-to-treat
IV	Intravenous
IVRS/IWRS	Interactive Voice/Web Response System
LAR	Legally acceptable representative
LC	Liquid chromatograph
LFU	Last follow-up
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
MS	Mass spectrometry

NOAEL	No-observed-adverse-effect level
NOEL	No-observed--effect level
PBP	Penicillin-binding protein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
QC	Quality control
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
T > MIC	Time that concentration is above the minimum inhibitory concentration
$t_{1/2}$	Elimination half-life
t_{max}	Time at which C_{max} is observed
TOC	Test-of-cure
VAP	Ventilator-associated pneumonia
Vss	Volume of distribution at steady state
WBC	White blood cell

1 BACKGROUND AND RATIONALE

1.1 Disease characteristics and treatment

Pneumonia is a leading cause of morbidity and mortality in children in developed countries (Lynch 2010, Shann 1999). Most cases of paediatric pneumonia are caused by viruses, typical bacteria, or atypical bacteria, with viral aetiology more common in younger patients, atypical bacteria (such as mycoplasma and chlamydia) most common in patients aged 5–15 years, and *Streptococcus pneumoniae* the most frequently identified of the typical bacteria (Lynch 2010, Michelow 2004).

The clinical signs and symptoms of viral and bacterial pneumonia are similar in children and cannot be reliably distinguished by use of any currently known combination of diagnostic tests (Lynch 2010). Viral diagnostic tests are reliable, commonly used, and may justify withholding antibacterial therapy (Bradley 2011), however, viral infection can predispose paediatric patients to bacterial co-infection (Woods 2013). In severe cases where a bacterial aetiology is suspected, therapy is generally empiric because pathogen identification often requires impractical invasive sampling (Blumer 1995). Accordingly, it is important to use antimicrobials that provide broad-spectrum antibacterial activity (Tam 2013, Parker 1995).

In adults, ceftobiprole is approved in the European Union (EU) for the treatment of hospital-acquired pneumonia (HAP), excluding ventilator-associated pneumonia (VAP), and for community-acquired pneumonia (CAP). In the paediatric population, the safety and efficacy of ceftobiprole have not yet been established.

This study is part of the approved EU Paediatric Investigation Plan (PIP) P/0083/2014 dated 4 April 2014 (see Appendix 1).

1.2 Investigational medicinal products

The treatment regimens to be administered are:

- Ceftobiprole medocaril sodium (ceftobiprole) 10 to 20 mg/kg administered intravenously (IV) q8h, age-adjusted for dose and infusion duration.
- Comparator for CAP: ceftriaxone 50 to 80 mg/kg IV as a single daily dose, up to a maximum dose of 2 g/day.
- Comparator for HAP: ceftazidime 50 mg/kg IV q8h, up to a maximum of 6 g/day.
- In patients receiving comparator antibiotics, administration of concomitant vancomycin (10 to 15 mg/kg IV q6h, up to a maximum dose of 2 g/day) is to be added when methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected or confirmed.

After a minimum of 3 days of treatment with systemic antibiotics (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 pre-defined criteria) may be switched to an oral antibiotic (age-appropriate for the paediatric patient) to complete a minimum of 7 days antibiotic treatment. A macrolide may be used for oral switch. The oral antibiotic will be recorded as a concomitant medication.

1.3 Nonclinical studies with ceftobiprole

1.3.1 Microbiology

Ceftobiprole has a strong affinity for several penicillin-binding proteins (PBPs), including PBP2a and PBP2x, which mediate resistance to other beta-lactams in staphylococci and pneumococci, respectively (Hebeisen 2001, Lovering 2012, Davies 2007, Davies 2010, Henry 2013, Entenza 2002). In contrast to earlier generation cephalosporins, ceftobiprole effectively prevents the intracellular growth of both MSSA and MRSA strains in macrophages and keratinocytes, due in part to its ability to better bind PBP2a under both neutral and acidic pH conditions (Lemaire 2009). Ceftobiprole also binds to and saturates several other essential PBPs (Davies 2010, Henry 2013), distinguishing it from other available beta-lactams, and is stable to hydrolysis by the *S. aureus* PC1 Class A beta-lactamase, conserving its activity against staphylococci (Queenan 2007).

Ceftobiprole is also relatively stable against AmpC cephalosporinases and common class A beta-lactamases produced by Gram-negative bacteria, but not to extended-spectrum beta-lactamases (ESBLs), carbapenemases, or OXA beta-lactamases (Queenan 2007).

In vitro single- and multiple-passage selection studies performed with several Gram-positive pathogens, including MRSA, demonstrated a very low propensity for resistance after exposure to ceftobiprole (Queenan 2007, Bogdanovich 2006, Queenan 2005, Kosowska 2005, Bogdanovich 2005, Queenan 2010), which is due to ceftobiprole's unique ability to bind to multiple target sites.

No emergence of resistance was seen throughout the extensive clinical development program and no minimum inhibitory concentration (MIC) shifts were seen in surveillance studies.

In vitro, ceftobiprole has shown a bactericidal mode of action against methicillin-susceptible *S. aureus* (MSSA), MRSA and many other resistant *S. aureus* strains, including glycopeptide-intermediate (GISA), vancomycin-intermediate (VISA), vancomycin-resistant (VRSA), daptomycin non-susceptible, and linezolid non-susceptible strains, using both broth microdilution and time-kill methods (Borbone 2010, Leonard 2008, Rouse 2007, Deshpande 2013, Farrell 2014).

Ceftobiprole also effectively reduced the colony-counts of MSSA and MRSA strains tested in an *in vitro* biofilm model, none of which were affected by daptomycin, vancomycin or rifampicin (Abbanat 2014).

Further details on the microbiology of ceftobiprole are provided in the Investigator's Brochure (IB).

1.3.2 Pharmacokinetics and product metabolism in animals

In animals after single-IV-dose PK studies, ceftobiprole medocaril was rapidly metabolised via non-specific esterases to ceftobiprole. The volume of distribution of ceftobiprole was restricted to the extracellular compartment, and its elimination occurred predominantly by passive glomerular filtration of unchanged ceftobiprole. The *in vitro*

and *in vivo* metabolic patterns of ceftobiprole in rats, dogs, mice, marmosets, and humans were similar, with the ring-open product BAL1029 as the main metabolite. After multiple doses to rats, rabbits, marmosets, cynomolgus monkeys, and dogs, high and dose-proportional exposures to ceftobiprole in all species were achieved, exceeding the expected human therapeutic exposure at the no-observed-adverse-effect level (NOAEL). There were no relevant indications of accumulation, differences related to sex, or time-dependent PK.

Whole-body autoradiography in animals demonstrated rapid and large distribution of ceftobiprole in all organs without specific accumulation in any organs, with the exception of the kidney as excretory organ. Results from a reproductive toxicology study in rats indicated that nursing pups were not systemically exposed to ceftobiprole. Protein binding of ceftobiprole in plasma in all species was low, and concentration-independent. Mean plasma protein binding in humans was 16%. In rats, excretion was almost complete (> 94%) within 4 days after IV administration of the prodrug.

Based on *in vitro* cytochrome P450 inhibition and induction data, the lack of a specific enzyme involved in cleavage of the prodrug, and ceftobiprole distribution being restricted to the extracellular compartment, the potential of ceftobiprole to exhibit clinically relevant enzyme-related drug-drug interactions is small.

In *in vitro* studies to determine whether ceftobiprole is a substrate or inhibitor of the efflux- or uptake-transporters, ceftobiprole inhibited OATP1B1 and OATP1B3 with median inhibitory concentrations of 67.6 µM and 44.1 µM, respectively, and ceftobiprole was found to be possibly a weak substrate of the renal uptake transporters OAT1 and OCT2. The clinical relevance of these findings is unclear.

Further details on the nonclinical pharmacology, PK, and PD of ceftobiprole are provided in the IB.

1.3.3 Toxicology

The primary targets of toxicity after IV administration in animals were the kidneys and the infusion site.

- Renal toxicity was attributable to the high rate of glomerular filtration leading to high concentrations of ceftobiprole in urine, precipitation of ceftobiprole in distal parts of the nephron, and resultant renal-tissue damage. This effect is not thought to apply to humans, because glomerular filtration of ceftobiprole in humans is much slower, and urinary concentrations of ceftobiprole do not approach the limit of solubility.
- Local tolerance: In 4- and 13-week studies in rats and marmosets, concentration-dependent slight-to-moderate local endothelial irritation was observed when ceftobiprole medocaril was administered into the *vena cava* over 4–8 hours at concentrations of up to 62 mg/mL.

  In a local tolerability study in rabbits, repeated IV administration of ceftobiprole into the auricular vein (8 consecutive days with a 3-minute endothelial contact period per day) caused no irritation at ceftobiprole concentrations of 2 and 10 mg/mL (nominal ceftobiprole medocaril concentrations of 2.66 and 13.3 mg/mL).

Hemolysis, plasma turbidity and precipitation were observed in human, dog, rat and marmoset blood at concentrations ≥12.5 mg/mL.

Ceftobiprole was neither teratogenic nor embryotoxic in rats and cynomolgus monkeys, and had no effects on fertility and early embryonic development in rats. No effects on behavioural or developmental parameters were noted in pups. No signs of skin sensitisation, irritation, or phototoxicity were seen. The antigenic potential of ceftobiprole is low. No mutagenic potential was seen in the Ames test or in the Chinese hamster ovarian assay. Positive effects in the mouse lymphoma/thymidine kinase and human chromosomal aberration tests *in vitro* were related to the cleavage product diacetyl, which is rapidly metabolised *in vivo*; the *in vivo* mouse micronucleus test and rat unscheduled DNA synthesis assays were negative. No genotoxic potential of impurities was identified. The convulsive potential after intracerebroventricular administration to mice was comparable to that of imipenem. No cardiac or pulmonary toxicities were observed.

Neonatal and juvenile rats (1 day old at start of dosing) given once-daily subcutaneous doses of ceftobiprole medocaril for 50 days exhibited similar findings to those seen in adults. Besides minor signs of local irritation at the injection site, the primary target of toxicity was the kidneys, with microscopic changes (cytoplasmic globules in collecting ducts) only at the highest dose of 250 mg/kg/day (corresponding to 187.5 mg/kg/day of ceftobiprole) and partial recovery after a 28-day recovery period. The NOAEL in juvenile animals was 100 mg/kg/day (corresponding to 75 mg/kg/day of ceftobiprole). At the NOAEL, a safety margin of 2 to 6 could be demonstrated for the recommended dosing regimens in the various age groups from neonates to < 18 years.

Safety margins based on plasma exposures noted at the NOAEL in animals are approximately 1- to 5-fold and 1- to 3-fold for maximum observed plasma concentration (C_{max}), and 2- to 3-fold and 1- to 2-fold for area under the concentration curve (AUC), respectively, for administration of 500 and 1000 mg ceftobiprole, infused to humans over 2 hours as ceftobiprole medocaril. The safety margins based on ceftobiprole plasma concentrations seen at the no-observed-effect level (NOEL) for renal toxicity are 2- to 7-fold and 1- to 5-fold relative to clinical doses of 500 and 1,000 mg. Relative to the clinical dose of 500 mg, the exposure ratio based on urine concentrations of ceftobiprole seen at the NOEL for renal toxicity is 4- to 34-fold.

These safety margins apply to both single-dose and multiple-dose administrations, as ceftobiprole accumulation is negligible with multiple dosing in humans.

Further details on the nonclinical toxicology of ceftobiprole are provided in the IB.

1.4 Clinical studies

1.4.1 Pharmacokinetics, product metabolism, and tissue distribution in humans

A retrospective population PK analysis of patients in the adult Phase 3 HAP study assessed the proportion of the dosing interval during which plasma ceftobiprole levels remained above the target MIC (*f*T>MIC), considering the highest MIC of either Gram-positive or Gram-negative microorganisms. This analysis demonstrated that the *f*T>MICs of 51.1% and 62.2% were associated with clinical cure and microbiological eradication, respectively (Muller 2014).

The PK of ceftobiprole in adult patients are predictable, linear, and time-independent across the dose range of 125 to 1000 mg, and variability is low (< 30%). Steady-state drug concentrations are attained on the first day of dosing (q8h), and no appreciable accumulation is observed in patients with normal renal function. The volume of distribution at steady state (Vss) of ceftobiprole is 18 L, suggesting that distribution is restricted to the extracellular water compartment. The total body clearance of ceftobiprole is approximately 5 L/h, and the apparent half-life ($t_{1/2}$) is 3 to 4 hours.

Ceftobiprole is eliminated primarily unchanged by renal excretion, with minimal metabolism to an open-ring metabolite, which accounts for approximately 4% of total exposure. The predominant mechanism responsible for elimination is glomerular filtration. The systemic clearance of ceftobiprole correlates with the creatinine clearance (CL_{CR}). Therefore dosing-regimen adjustments are recommended in adult patients with moderate and severe renal impairment, in end-stage renal disease (ESRD) patients and in patients with creatinine clearance CL_{CR} > 150 mL/min. At comparable CL_{CR}, the PK of ceftobiprole in patients in an intensive care unit (ICU) setting and in patients from the HAP and CAP studies are similar to healthy subjects. Given no underlying renal impairment, the primary PK/PD driver of ceftobiprole (T>MIC) is unaffected by gender, obesity, age, or race, and no dose adjustment is required in these sub-populations.

The distribution of ceftobiprole in lung epithelial lining fluid, bone, muscle and adipose tissue is similar to that of other cephalosporins.

Following administration of 500 mg ceftobiprole q8h for 7 days, ceftobiprole could not be detected in the faeces of healthy subjects, there were no significant changes in the aerobic or anaerobic intestinal microflora, and no new colonising aerobic or anaerobic bacteria resistant to ceftobiprole were observed.

In paediatric patients given single doses of ceftobiprole at 15 mg/kg (ages 3 months to < 6 years) or 10 mg/kg (ages 6 years to < 12 years), the single-dose PK of ceftobiprole were generally within the range of those previously observed in healthy adult subjects after a single ceftobiprole 500 mg administration. However, in patients given 7 mg/kg (ages 12 years to < 18 years), the systemic exposure was substantially lower than that achieved in adults after a single ceftobiprole 500 mg dose. The extent of conversion of the prodrug was demonstrated *in vivo* and *in vitro* to be age-independent from neonates to adults.

1.4.2 Pharmacodynamics

In animal models of efficacy (bacteriostasis), ceftobiprole *f*T>MICs of > 30% and > 50% are required for susceptible Gram-positive and Gram-negative pathogens, respectively, at a target MIC of 4 µg/mL. For 1 log-kill in colony forming units (CFU) (bactericidal effect) in animal pneumonia and thigh models, the target *f*T>MIC of 4 µg/mL remains > 30% for susceptible Gram-positive pathogens, and > 60% for susceptible Gram-negative pathogens.

In adults, the recommended clinical dosing regimen for ceftobiprole is 500 mg q8h, administered as a 120-minute IV infusion. A retrospective population PK analysis of patients in the Phase 3 HAP study demonstrated that for a 60% *f*T>MIC of 4 µg/mL, the probability of target attainment under this regimen is 100% for Gram-positive pathogens and > 96% for Gram-negative pathogens.

1.4.3 Susceptibility testing breakpoints

Minimum inhibitory concentration breakpoints for ceftobiprole established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), are shown in Table 1.

Table 1 Ceftobiprole MICs established by EUCAST

Organisms	MIC breakpoints (mg/L)	
	Susceptible (≤ S)	Resistant (R >)
Staphylococcus aureus (including MRSA)	2	2
Streptococcus pneumoniae	0.5	0.5
Enterobacteriaceae	0.25	0.25
Pseudomonas aeruginosa	IE [a]	IE [a]
Non-species specific breakpoint [b]	4	4

[a] Insufficient evidence.
[b] Based on the *f*T>MIC target of 50% and >90% target attainment rate.

1.4.4 Efficacy in hospital-acquired pneumonia

In a Phase 3 HAP study (BAP248/307, Awad 2014), the non-inferiority of ceftobiprole to ceftazidime plus linezolid was demonstrated within the pre-specified 15% margin for the primary efficacy endpoint of clinical cure rate at the test-of-cure (TOC) visit for all subjects in the clinically-evaluable (CE) and intent-to-treat (ITT) analysis sets. The ITT analysis set included 391 patients in the ceftobiprole group and 390 patients in the comparator group.

The clinical cure rates at the TOC visit were 69.3% and 71.3% (CE), and 49.9% and 52.8% (ITT) in the ceftobiprole and linezolid plus ceftazidime groups, respectively.

Non-inferiority of ceftobiprole to linezolid plus ceftazidime was also demonstrated in the pre-specified subgroup of subjects with HAP (excluding VAP) (N=571). Non-inferiority of ceftobiprole was not demonstrated in the smaller subset of VAP subjects (N=210).

1.4.5 Efficacy in community-acquired pneumonia

The results of the Phase 3 CAP-3001 study (Nicholson 2012) demonstrated the non-inferiority of ceftobiprole 500 mg administered q8h as a 2-hour infusion to treatment with ceftriaxone with or without linezolid for subjects hospitalized with CAP within the pre-specified margin of 10% for the primary efficacy endpoint of clinical cure rate at the TOC visit. ITT analysis set comprised 314 patients in the ceftobiprole group and 324 patients in the comparator group.

The clinical cure rates at the TOC visit in the ceftobiprole and ceftriaxone with or without linezolid groups, respectively, were 86.6% and 87.4% in the clinically evaluable (CE) analysis set, and 76.4% and 79.3% in the ITT analysis set. The respective clinical cure rates in patients in PORT Risk Classes ≥ III (PSI score ≥ 71) were 86.5% and 86.3% (ITT), and 79.1% and 78.5% (CE).

1.4.6 Safety

The current safety experience from clinical studies of ceftobiprole comprises 3037 subjects (1404 from Phase 3 pneumonia studies, 1633 from Phase 2 and Phase 3 cSSTI studies, and 511 subjects from Phase 1 studies). The observed safety profile is consistent with that of the cephalosporin class as a whole.

The most common adverse reactions, occurring in ≥ 3% of patients treated with ceftobiprole were nausea, vomiting, diarrhoea, infusion-site reactions, hypersensitivity (including urticaria, pruritic rash, and drug hypersensitivity), and dysgeusia.

Less frequently reported, but more serious adverse reactions included thrombocytopenia, agranulocytosis, anaphylaxis, *Clostridium difficile* colitis, convulsion, agitation (including anxiety, panic attacks, and nightmares), and renal failure.

In a previous clinical study in 64 paediatric patients age 3 months to 17 years (study CSI-1006), ceftobiprole was administered IV at a concentration of 2 mg/mL as a single dose over 2-hours (at dose levels of 7, 10, or 15 mg/kg). In this study, ceftobiprole was well tolerated, with vomiting reported as the most frequent adverse event (AE) (6/64 patients). The majority of AEs were mild in severity and considered not related to study drug. No deaths and no ceftobiprole-related serious adverse events (SAEs) were reported during the study, and no patients discontinued due to a treatment-emergent AE.

In terms of local tolerability, 1 moderate catheter-site-related reaction was observed in a child in the age group 2 to < 6 years (ceftobiprole 15 mg/kg) and 1 mild phlebitis in a child in the age group 3 months to < 2 years (ceftobiprole 15 mg/kg). Overall, the available preclinical and clinical data suggest that the expected risk of local irritation in the paediatric population with ceftobiprole is acceptable, but should be carefully monitored.

Detailed warnings and precautions related to ceftobiprole are provided in the IB.

The safety profiles of the standard-of-care comparators in children are well characterised due to their use over many years, and are described in the respective SmPCs.

1.5 Rationale for study design and dosing regimens

1.5.1 Study design rationale

The study design is adequate to identify the most common AEs associated with ceftobiprole in the two age groups of patients < 6 years and ≥ 6 years, and adequate to describe the efficacy of ceftobiprole in paediatric patients with HAP or CAP. Blood sampling is minimal, but adequate to monitor safety and provide PK information through PK sampling. Safety measures include the selection of clinics experienced in paediatric care.

Treatment of 92 patients (the Safety population) with ceftobiprole will yield a > 95% probability of observing at least one AE type if the actual probability of this event is > 3.2%.

In addition, the investigator-blinded nature of the study will allow for an unbiased assessment of the safety profiles of the study treatments.

The dosing regimen of ceftobiprole (10 to 20 mg/kg, up to a maximum of 500 mg, given q8h as 2-hour or 4-hour infusions) provides adequate exposure for eradication of pathogens likely to be present in the enrolled patients. The selected comparator antibiotics and regimens are standard-of-care cephalosporin treatments, with the addition of vancomycin if MRSA is suspected or confirmed.

1.5.2 Study drug and dose

1.5.2.1 Ceftobiprole medocaril

Patients will receive 10 to 20 mg/kg ceftobiprole, up to a maximum of 500 mg, administered as 2-hour or 4-hour continuous-rate infusions of ceftobiprole medocaril q8h, for a minimum of 3 days. Treatment may be prolonged up to a maximum of 14 days.

The age-adjusted ceftobiprole medocaril doses and infusion times are provided in Section 6.1.1.

A detailed dosing rationale is provided in Appendix 1. In summary, the planned dose of ceftobiprole is based on the results of study CSI-1006, in which paediatric patients aged 3 months to < 18 years received 7 to 15 mg/kg as a 2-hour infusion. In addition, the dosing regimen (dose, dosing interval and infusion duration) was designed for paediatric patients aged 3 months to < 18 years to ensure that the *f*T>MIC at 4 µg/mL is > 50%, and to maintain the exposure within the adult well-tolerated range and below the NOAEL in the juvenile rat study TOX8611 for the corresponding age groups.

1.5.2.2 Comparators

The dosing regimens for the the standard-of-care comparators are provided in Section 6.1.2.

2 OBJECTIVES OF THE STUDY

2.1 Primary objective

The primary objective of this study is to characterise the safety profile of ceftobiprole in paediatric patients with HAP or CAP requiring hospitalisation and IV antibiotic therapy.

2.2 Secondary objectives

The secondary objectives of this study are in paediatric patients with HAP or CAP requiring hospitalisation:

- To compare the clinical cure rate and microbiological eradication rate at the 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 PK of ceftobiprole

3 STUDY DESIGN

3.1 Overview of study design and dosing regimens

This is a randomized, investigator-blind, multiple-fixed dose, active-controlled multicentre study to be carried out in 138 paediatric patients (minimum of 125 evaluable patients) aged 3 months to < 18 years diagnosed with either HAP or CAP requiring hospitalisation and treatment with systemic 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. Patients will be randomized 2:1 within each group to receive either ceftobiprole or the comparator standard-of-care IV cephalosporin antibiotic (ceftazidime with or without vancomycin for patients with HAP; ceftriaxone with or without vancomycin for patients with CAP). At least 50 patients are planned to be enrolled in each of the age categories < 6 years and ≥ 6 years (see Sections 6.3 and 8.1). There is no requirement for a minimum number of patients with each infection type (HAP or CAP).

Table 2 Summary of treatment and follow-up schedule

Study phase				
1	**2**	**3**		**4**
Pre-treatment	**Active treatment**	**Post-treatment**		**Follow-up**
Screening and randomization	**Study drug followed by optional oral treatment**	**End of treatment (EOT)**	**Test-of-cure (TOC)**	**Last follow-up (LFU)**
Day −1 Baseline	From Day 1 At least 7 days, up to 14 days.	Within 24 hours after last treatment	7–14 days after last treatment	28–35 days after last treatment

The study comprises the following phases (Table 2):

- A pre-dosing screening phase of up to 24 hours
- A treatment phase of 7 days, with possible prolongation up to 14 days, with IV administration of ceftobiprole or appropriate comparator treatment, with the option for oral switch after a minimum of 3 days (nine infusions) of IV treatment
- A post-treatment TOC assessment 7 to 14 days after the last treatment
- An LFU assessment 28 to 35 days after the last treatment to monitor relapse of pneumonia, and safety

The total duration of the study for each patient is approximately 5–7 weeks.

Study assessments are summarised in the Schedule of assessments (Table 4) and outlined in more detail in Section 5. After randomization and during active treatment, patients will receive ceftobiprole or standard-of-care comparator (± vancomycin) according to the schedule outlined in Table 3.

Table 3 Study-drug administration

Study drug	Dose (mg/kg)	Concentration (mg/mL)	Frequency	Infusion duration (h)	Maximum daily dose (mg)
Ceftobiprole	10–20	2–4	q8h	2–4	1500
Ceftriaxone	50–80	20	q24h	0.5	2000
Ceftazidime	50	20	q8h	0.5	6000
Vancomycin	10–15	4	q6h	1	2000

3.2 Endpoints

3.2.1 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.

3.2.2 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 and LFU visits; 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).

3.3 Treatment plan

Once a patient is randomized, IV study medication should be administered as soon as possible, with preferably no more than 6 hours between randomization and first study-drug administration. Pharmacy and centre staff will be unblinded to treatment. Each centre will implement a Study Blinding Plan to ensure that blinded investigators remain blinded to the assigned treatment (see Section 6.3).

Details of the study treatments to be administered, including dosages, are provided in Section 1.2.

Patients will receive IV antibiotics for at least 3 days (9 infusions); at the discretion of the Blinded Investigator, patients may switch to oral antibiotics after 3 days (9 infusions) if they meet standardized criteria of clinical improvement (see Section 3.4).

Treatment (IV or oral) will continue for a minimum of 4 additional days (total of 7 days treatment). If required, a prolongation of treatment, up to a total of 14 days of treatment, is possible.

Patients who require concomitant treatment with a macrolide during the course of the active IV study drug treatment period (other than as part of a switch to oral antibiotic treatment, see Section 3.4) should be withdrawn from the study and treated with an appropriate non-study standard-of-care antibiotic regimen.

3.4 Intravenous-to-oral switch

After a minimum of 3 days of study treatment (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 may be switched to an oral antibiotic to complete a minimum of 7 days antibiotic treatment, at the discretion of the Blinded Investigator.

No oral formulations of the study antibiotics are available. The choice of oral antibiotic will be at the discretion of the Blinded Investigator, taking into consideration local standards of care and antibiotic susceptibility patterns.

Recommended options for an oral switch are penicillins (amoxicillin ± clavulanate), cephalosporins (cefuroxime axetil, cefaclor, cephalexine), macrolides (erythromycin, azithromycin, clarithromycin, roxithromycin), clindamycin, and linezolid.

The oral antibiotic is to be recorded as a concomitant medication.

All of the following criteria must be met for at least 24 hours at the time of the IV to oral antibiotic switch:

1. The patient has a normally functioning gastrointestinal tract and the ability to swallow an age-appropriate formulation of the intended oral antibiotic.
2. The patient demonstrates clinical improvement such that, in the opinion of the Blinded Investigator, a step-down to oral antibiotic therapy is medically appropriate.

3. Either:
   (a) The causative pathogen for pneumonia has been identified and confirmed as susceptible to the intended oral antibiotic regimen.
   or
   (b) In the opinion of the Blinded Investigator, and based on local antibiotic susceptibility data, likely causative pathogens for the relevant type of pneumonia (HAP or CAP) are expected to be susceptible to the intended oral antibiotic regimen.
4. The patient has stable (or baseline) mental status.
5. The patient displays appropriate appetite and activity level.
6. Oxygen saturation > 92% on room air by pulse oximetry on at least four separate occasions within 24 hours, with no measurements indicating oxygen saturation ≤ 92%.
7. Body temperature < 37.8 °C on at least four separate occasions within 24 hours, with no measurement indicating temperature ≥ 37.8 °C.

3.5 Home continuation of oral antibiotic therapy

Patients switched to oral antibiotic therapy may remain inpatients, or be discharged home to be followed up as outpatients, at the discretion of the Blinded Investigator.

All of the following criteria must be met for home continuation of antibiotic treatment:

1. The patient demonstrates clinical improvement such that, in the opinion of the Blinded Investigator, home discharge is medically appropriate.
2. The Blinded Investigator considers the patient's parent(s) or legally acceptable representative (LAR) capable of administering, or supervising the administration of, (as appropriate to the patient's age) oral antibiotics in accordance with the dosing instructions.
3. The patient is able to comply with taking the medication.
4. The Blinded Investigator considers the patient's home environment to be safe, with continuous, adequate, and appropriate care by a competent adult available at all times.
5. Instructions for promptly returning to the study centre in the event of clinical deterioration are provided to the patient's parent(s) or LAR.

3.6 Concomitant and previous medication and treatment

All medication given to the patient during the course of the study is to be recorded in the case report form (CRF); information to be recorded includes the trade name of the medication, the indication, the dose and frequency of treatment, and the start and stop dates of treatment. Changes in the dose or schedule of a given medication must also be recorded in the CRF.

Medication given within 14 days before Screening up to the start of study drug dosing is defined as prior medication; if given after the start of study drug dosing, up to the LFU visit safety assessment 28 to 35 days after the EOT visit, it is defined as concomitant medication.

As described in the following sections, patients may receive treatment for suspected or proven infection with *Pseudomonas aeruginosa* (see Section 3.6.2), in addition to ceftobiprole or standard-of-care comparator antibiotics (plus vancomycin), if clinically required. Patients may also receive non-antimicrobial medication and treatment. 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) should be withdrawn from study treatment (see Section 4.4). Oral macrolides are permitted for patients switching from IV study drug to oral standard-of-care antibiotics, according to predefined criteria after at least 9 infusions of IV study drug administration (see Section 3.4).

3.6.1 Concomitant anti-staphylococcal treatment in patients with HAP or CAP

In patients receiving comparator antibiotics, vancomycin is added when MRSA is suspected or confirmed (see Sections 6.1.2.1 and 6.1.2.2). Patients treated with ceftobiprole are not to receive concomitant vancomycin or other anti-staphylococcal treatment as part of the study medication (see Section 6.1.1).

Patients treated with ceftobiprole who require additional anti-staphylococcal treatment (e.g., due to clinical failure), or patients in the standard-of-care comparator group who require anti-staphylococcal treatment other than vancomycin, should be discontinued from the study and treated as clinically indicated.

3.6.2 Anti-pseudomonal treatment in patients with HAP or CAP

Anti-pseudomonal treatment may be added to ceftobiprole treatment and/or standard-of-care comparator treatment if clinically indicated (see Section 3.3).

Anti-pseudomonal treatment for both the ceftobiprole and standard-of-care comparator group should comprise:

- amikacin: 15–22.5 mg/kg per day in 1–3 divided doses
- gentamicin: 4.5–7.5 mg/kg per day in 1 dose (preferred) to 2 divided doses
- tobramycin: 6–7.5 mg/kg per day in 3–4 equally divided doses

3.6.3 Macrolide treatment in patients with HAP or CAP

Patients with documented or suspected atypical bacterial pneumonia are to be excluded from the study (see Section 4.3).

Patients who require concomitant treatment with a macrolide during the course of the active IV 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. All such cases should be classified as clinical failure (see Section 5.3.2).

The use of an oral macrolide for IV to oral switch according to predefined criteria after at least 72 hours of IV study drug administration (see Section 3.4) is permitted.

3.7 End of study definition

The end of the study is defined as the completion of the last study-related contact with any patient (last patient last visit).

4 STUDY POPULATION

4.1 Target population

The target population comprises male or female paediatric patients aged 3 months to < 18 years with HAP or CAP requiring hospitalisation and treatment with IV antibiotics.

4.2 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 (ICU), 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 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 intravenous antibacterial treatment for pneumonia
6. Sufficient vascular access to receive IV study drug
7. Informed consent from the parent or legally acceptable representative 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

4.3 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 the time of 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)

4.4 Discontinuation of treatment

Patients who require concomitant treatment with a macrolide during the course of the active IV 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. If possible, these patients should complete EOT, TOC, and LFU assessments.

A patient must be discontinued from study treatment if any of the following events occur:

- no adequate response to the antibiotic treatment within 3 days of treatment
- need for the use of macrolides concomitant to study drug treatment
- pregnancy

All reasons for discontinuation of treatment must be recorded by the Blinded Investigator. In addition to those above, such reasons may include:

- adverse event
- abnormal laboratory value
- abnormal test procedure result
- intercurrent illness that prevents or interfere with further administration of treatment
- death
- protocol deviation
- lost to follow-up
- administrative/logistical reasons

For all patients who discontinue study treatment, AE monitoring must be continued up to and including an LFU visit 28 to 35 days after EOT.

Patients who discontinue from study treatment should be encouraged to remain on study to complete the post-treatment EOT, TOC, and LFU visits.

For patients who fail to return for EOT, TOC, or LFU visits, the Blinded Investigator must make every effort to contact the patient (by telephone or mail correspondence). The outcome of this contact must be documented by the Blinded Investigator in the patient's source documents. The reasons for failing to return for the visits must be recorded in the case report form (CRF).

4.5 Discontinuation from the study

Patients may withdraw from the study at any time and for any reason. Parents or LARs may also withdraw consent for the patient's participation at any time and for any reason.

The Blinded Investigator may also withdraw patients (e.g., in case of treatment failure, adverse reactions, poor compliance, or for administrative reasons).

If patients are withdrawn, the date of withdrawal, the number of infusions completed up to that date, and the reason for withdrawal must be recorded in the CRF. If an infusion is stopped, the exact time of the termination must be recorded in the CRF.

Blinded Investigators are encouraged to recommend that patients discontinued from treatment complete the EOT, TOC, and LFU assessments.

4.6 Replacement of patients

The following patients are to be replaced:

- Patients failing screening procedures are to be replaced.
- Patients who discontinue participation in the study for any reason after randomization but before receiving the first dose of study drug are to be replaced.

The following patients are not to be replaced:

- Patients who discontinue participation in the study for any reason after receiving the first dose of study drug are not to be replaced.

Patients who fail screening procedures, patients discontinued from the study, and patients who have completed the study, are not permitted to re-enroll in the study.

5 SCHEDULE OF ASSESSMENTS AND PROCEDURES

5.1 Summary schedule of assessments

Table 4 presents a summary of the assessments to be performed from Screening to the final post-treatment visit.

Table 4 Schedule of assessments

Assessment / **Study Day**	**Screening** Day −1 to 1	**Active treatment** Day 1	Days 2–3	Day 4	Days 5–7	Day 8–14	**EOT***	**TOC** 7–14 days after EOT	**LFU**** 28–35 days after EOT
Written informed consent[1]	X								
Inclusion/exclusion criteria	X								
Medical history and demographics	X								
Prior medications[2]	X								
Pregnancy test[3]	X						X		
Physical examination	X			X			X		
Laboratory tests[4]	X			X			X	X	
Haptoglobin[5]	X			X			X		
Direct antiglobulin (Coombs) test[6]	X							X	
Vital signs and pulse oximetry[7]	X	X	X	X	X	X	X	X	
Pneumonia signs and symptoms	X	X	X	X	X	X	X	X	
Clinical pneumonia outcome assessment[8]				X			X		
Study medication		X	X	X	X	X			
Eligibility for IV to oral switch				X	X	X			
Concomitant medication[9]		X	X	X	X	X	X	X	X
Adverse events[10]		◄----- continuous from time of first study drug administration------►							
Imaging[11]	X								
Microbiological sampling[12]	X						X	X	X
Overall microbiological outcome								X	X
Overall clinical outcome[13]								X	X
PK sampling[14]			X						
Treatment/hospitalisation setting	X	X	X	X	X	X	X	X	X

[1] The informed consent form (and the assent form where appropriate) must be signed before any study procedures take place (see Section 10.2).

[2] Prior medications taken up to 14 days before Screening are to be recorded.

[3] Pregnancy testing must be conducted for all menarcheal female patients. If results of the pregnancy test are positive at Screening, the patient must not be randomized in the study.

[4] Laboratory tests include haematology, biochemistry, and urinalysis (see Section 5.6.2).

[5] For children aged 6 years and older and in younger patients not treated with vancomycin.

[6] For children aged 6 years and older and in younger patients not treated with vancomycin.

[7] Vital signs (including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) and pulse oximetry must be recorded three times daily during the active study drug treatment period. Vital signs and pulse oximetry must also be obtained at the EOT visit and the TOC visit. Weight will be assessed at Screening, and EOT. Height is to be assessed only at Screening (See Sections 5.6.3 and 5.6.4).

[8] On Day 4 and at the EOT visit, the Blinded Investigator must make an overall clinical assessment of pneumonia as being worsened, unchanged, improved, or cured.

[9] All medications taken since the recording of prior medications, and medications continued at entry into the study, should be recorded as concomitant therapy.

[10] Non-serious changes in, or worsening of, a patient's condition that occur between informed consent and first study-drug administration are to be collected as pre-dose medical history. If any such occurrence is considered to be serious, it will additionally be reported following the procedures of an SAE, to allow for an assessment of serious procedure-related events. All AEs occurring from the time of first study-drug administration to the LFU visit must be collected in accordance with the procedures outlined in Section 7.

[11] Screening imaging (e.g., X-ray, ultrasound, or computer tomography) does not need to be repeated if it was performed within 24 hours of informed consent; post-baseline imaging may be obtained as clinically indicated.

[12] Blood samples for culture and Gram stain are to be obtained at Screening if feasible. Post-baseline blood cultures should be obtained as clinically indicated according to local practice during therapy, at EOT, and at the TOC. At the LFU visit, sampling is only to be undertaken if considered necessary by the Blinded Investigator to evaluate microbiological relapse (need for further antibiotic treatment).

[13] At the TOC visit, the Blinded Investigator must rate the overall clinical outcome of therapy as clinical cure, clinical failure, or clinically unevaluable. At the LFU visit, for patients with TOC outcomes of clinical cure, an assessment of relapse must be performed (see Section 5.2.7).

[14] Blood samples (200–300 µL) are to be taken on Day 3 at the following time points: Children aged 2 years and older – pre-dose, and at 2h (end of infusion), 4h, 6h, and 8h after start of infusion; children aged less than 2 years – pre-dose and at 4h (end of infusion), 6h, and 8h after start of infusion.

[*] EOT assessment is to be performed within 24 hours after the last study drug administration. If a patient withdraws prematurely, EOT visit laboratory/safety tests are to be conducted within 1 week of patient's withdrawal.

[**] The LFU visit will be performed by telephone contact unless an examination is needed to evaluate relapse or abnormalities at the TOC assessment (see Section 5.2.7). The overall clinical outcome of relapse will only be assessed for patients with an outcome of 'clinical cure', and the assessment of microbiological relapse will only be performed for patients with outcomes of 'microbiological eradication' or 'presumed microbiological eradication'.

5.2 Study visits

5.2.1 Screening (Days −1 to 1)

The parents or LARs must provide written informed consent for patients to participate in the study before any study-specific procedures are carried out. Age-appropriate assent procedures for the paediatric patients may also be necessary, as described in Section 10.2.

Once informed consent (and assent, as applicable) is obtained, patients are considered enrolled in the study and are to be screened within 24 hours prior to the first dose of study medication. Screening evaluations and dosing may be performed on the same day (Day 1). Analyses required as part of the screening process which have been performed within the 24 hours prior to dosing do not need to be repeated, regardless of whether they were performed before or after signing of the ICF.

Screening will comprise:

- Medical history and demographics
- Review and recording of medication given within the previous 14 days
- Pregnancy testing must be conducted on all menarcheal female patients
- Physical examination
- Safety laboratory tests (central laboratory, see Section 5.6.2). Local laboratory results may be used for inclusion and exclusion criteria.
- Vital signs (including height and weight, body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) (see Section 5.6.3)
- Measurement of oxygen saturation (pulse oximetry; see Section 5.6.4)
- Rating of the signs and symptoms of pneumonia (see Section 5.3.1)
- Chest imaging (e.g., X-ray, ultrasound, or computer tomography), unless this has been performed within 24 hours of informed consent
- Collection and culture of microbiological respiratory samples (and blood culture if clinically indicated) (see Section 5.4)
- Treatment setting/hospitalisation (ICU or other ward)

Based on the screening results, the investigator will review all enrolment criteria, including laboratory test results, to ensure patient eligibility.

5.2.2 Start of treatment (Day 1)

Patients will be randomized to treatment with ceftobiprole or comparator. Start of study drug administration should be performed as soon as possible thereafter, and no later than 6 hours after randomization.

Clinical signs and symptoms of pneumonia are to be rated by the Blinded Investigator before the start of dosing (see Section 5.3.1).

Ceftobiprole medocaril will be reconstituted, diluted for IV administration, and administered as described in Section 6.2. Comparator antibiotics will be administered according to the manufacturer's instructions, the Pharmacy Manual, and consistent with local standard practice. The dates and exact start and stop times of all infusions must be recorded in the CRF.

Anti-staphylococcal treatment should be given as described in Section 3.6.1. Anti-pseudomonal treatment may be given as indicated (see Section 3.6.2).

Vital signs and measurement of oxygen saturation (pulse oximetry) must be recorded before the start of the first dose of study drug, and every 8 hours thereafter (see Section Table 4 and Section 5.6.4).

Changes in medication must be recorded. Information on the treatment setting (ICU or other ward) must be documented in the CRF. Adverse events must be monitored and recorded by the Blinded Investigator on Day 1 and throughout the study (see Table 4 and Section 7).

Additional microbiological sampling or chest X-rays will not be required for study purposes, however, results from microbiological blood culture or respiratory sampling or from additional chest X-rays performed in the context of routine clinical care must be documented in the CRF.

5.2.3 Days 2 to 7 (active treatment)

All days 2–7

The Blinded Investigator must rate the clinical signs and symptoms of pneumonia on each day (during a study-drug-free interval in the morning in order to maintain blinding) (see Section 5.3.1). Vital signs and measurement of oxygen saturation (pulse oximetry) must be recorded before the first dose of antibiotics is given, and every 8 hours thereafter. Changes in medication must be recorded. Information on the treatment setting (ICU or other ward, or from Day 4, ambulatory treatment) must be documented in the CRF. AEs must be monitored and recorded by the Blinded Investigator (see Table 4 and Section 7).

Additional microbiological sampling or chest X-rays is not required for study purposes, however, results from microbiological blood culture or respiratory sampling or from additional chest X-rays performed in the context of routine clinical care must be documented in the CRF.

Blood samples must be obtained for the determination of plasma levels on Day 3 (see Section 5.5.1 for instructions on sample preparation). From study Day 4 onwards (after a minimum of 3 days (9 infusions) of treatment with systemic study antibiotics) patients will be assessed daily by the Blinded Investigator for eligibility for an IV to oral switch.

If IV study antibiotics are given from Day 4 or later (see below), ceftobiprole medocaril or comparator antibiotics are to be administered as on Day 1 (see Section 5.2.2). The dates and exact start and stop times of all infusions must be recorded in the CRF.

If oral antibiotics are given from Day 4 or later, the dates and times of administration must be recorded in the CRF (see Section 3.4).

Anti-pseudomonal treatment may be given as indicated (see Section 3.6.2).

Day 4 only

After 3 days (9 infusions) of treatment with IV study antibiotics, if clinical signs and symptoms are absent or improved, the Blinded Investigator may consider switching the patient from systemic to oral antibiotic therapy (see Section 3.4). In the absence of substantial clinical improvement, the Blinded Investigator should consider changes in therapy or withdrawal of the patient from the study.

On Day 4, a physical examination must be performed, and the Blinded Investigator must also make an overall clinical assessment of pneumonia as being worsened, unchanged, improved or cured.

Safety laboratory tests must also be obtained on Day 4 (see Section 5.6.2).

5.2.4 Days 8 to 14 (active treatment)

Clinical signs and symptoms of pneumonia must be rated by the Blinded Investigator each day (see Section 5.3.1). If clinical signs and symptoms are absent or sufficiently improved on Day 8, the Blinded Investigator may consider stopping antibiotic therapy at any time after treatment for a minimum of 7 days.

If antibiotic therapy is continued, clinical signs and symptoms of pneumonia must be rated by the Blinded Investigator each subsequent day (during a study drug free interval in the morning in order to maintain blinding) (see Section 5.3.1). Whenever clinical signs and symptoms are absent or improved, the Blinded Investigator may consider stopping antibiotic therapy.

Patients are to be assessed daily by the Blinded Investigator for eligibility for an IV to oral switch.

If IV study antibiotics are given from Day 4 or later, ceftobiprole medocaril or comparator antibiotics are to be administered as on Day 1 (see Section 5.2.2). The dates and exact start and stop times of all infusions must be recorded in the CRF.

If oral antibiotics are given from Day 4 or later, the dates and times of administration must be recorded in the CRF (see Section 3.4).

Anti-pseudomonal treatment may be given as indicated (see Section 3.6.2).

Vital signs and measurement of oxygen saturation (pulse oximetry) must be recorded before the start of the first dose of study drug administration, and every 8 hours thereafter.

Any other changes in medication must be recorded. Information on the treatment setting (ICU, other ward, or ambulatory treatment) must be documented in the CRF. AEs must be monitored and recorded by the Blinded Investigator (see Table 4 and Section 7).

Additional microbiological sampling or chest X-rays are not required for study purposes, however, results from microbiological blood culture or respiratory sampling or from additional chest X-rays performed in the context of routine clinical care must be documented in the CRF.

The maximum duration of study drug administration is 14 days.

5.2.5 End-of-treatment (EOT)

EOT assessments are to be performed within 24 hours after administration of the last dose of IV or oral antibiotics. The recommended minimum duration of antibiotic intake is 7 days (including both study drug and oral switch, as applicable). The maximum duration of study drug administration (if no oral switch is used) is 14 days.

A physical examination (including body weight) must be performed.

The Blinded Investigator must rate the clinical signs and symptoms of pneumonia (see Section 5.3.1). The Blinded Investigator must also make an overall clinical assessment of pneumonia as being worsened, unchanged, improved or cured.

Vital signs and pulse oximetry results must be recorded, and blood and urine samples for laboratory safety tests must be obtained at this visit. Pregnancy testing must be conducted on all menarcheal female patients.

Where possible, microbiological samples should be collected and cultured as described in Section 5.4.

Changes in medication must be recorded. Information on the treatment setting (ICU, other ward, or ambulatory treatment) must be documented in the CRF. AEs must be monitored and recorded by the Blinded Investigator at the EOT visit (see Table 4 and Section 7).

Chest X-rays are not required for study purposes, however, results from additional chest X-rays performed in the context of routine clinical care must be documented in the CRF.

5.2.6 Test-of-cure (TOC)

TOC assessments must be performed 7 to 14 days after the EOT evaluation. The Blinded Investigator must rate the clinical signs and symptoms of pneumonia, and the overall clinical outcome of therapy (see Section 5.3.2).

Vital signs and pulse oximetry results must be recorded, and blood and urine samples for laboratory safety tests must be obtained at this visit.

Where possible, microbiological samples should be collected and cultured as described in Section 5.4.

Overall microbiological outcome will be assessed by the Blinded Investigator in accordance with the definitions in Section 5.3.3.

Changes in medication must be recorded. Information on the treatment setting (ICU, other ward, or ambulatory treatment) must be documented in the CRF. AEs must be monitored and recorded by the Blinded Investigator at the TOC visit (see Table 4 and Section 7).

Chest X-rays will not be required for study purposes, however, results from additional chest X-rays performed in the context of routine clinical care must be documented in the CRF.

5.2.7 Last follow-up

An LFU assessment must be performed 28 to 35 days after the EOT evaluation for all patients, and may comprise a clinic visit or a telephone contact conducted by medically qualified staff as appropriate. Information on the treatment setting (ICU, other ward, or ambulatory treatment) must be documented in the CRF.

The LFU visit must include monitoring and recording of AEs (see Section 7) and concomitant medications for all patients.

For patients with TOC outcomes of clinical cure an assessment of relapse must be performed as follows:

- If a clinic visit is scheduled, the Blinded Investigator is to evaluate signs and symptoms of pneumonia (see Section 5.3.1) and the need for further antibiotic therapy for pneumonia, and record the outcome as ‘clinical relapse’ or ‘clinical cure maintained’.
- If the patient (or a parent/LAR) denies any signs and symptoms of respiratory illness in a telephone interview, and requests no medical attention, the outcome is to be classified as ‘clinical cure maintained’.
- If the patient (or a parent/LAR) reports or confirms signs and symptoms of respiratory illness in a telephone interview, a clinic visit is to be scheduled for evaluation of the signs and symptoms of pneumonia. If the patient does not attend the clinic visit, further telephone contact must be attempted in order to establish recovery (absence of respiratory illness) without antibiotic therapy (outcome: ‘clinical cure maintained’) or if systemic antibiotics were used for the treatment of pneumonia (outcome: ‘clinical relapse’).

Chest X-rays are to be obtained, if clinically indicated, in relapsing patients who require further antibiotic therapy for pneumonia at the discretion of the Blinded Investigator. Where possible, microbiological samples should also be collected and cultured. Blood culture sampling is only to be undertaken if considered necessary by the Blinded Investigator, to evaluate microbiological relapse (see Section 5.4).

If applicable, overall microbiological outcome will be assessed by the Blinded Investigator in accordance with the definitions in Section 5.3.3.

5.3 Efficacy evaluations

5.3.1 Pneumonia signs and symptoms and requirement for hospitalisation

The Blinded Investigator is to rate the following 10 signs and symptoms as 'absent' or 'present' at baseline (pre-dose), and as 'absent', 'improved', 'unchanged', or 'worsened', on every day of active treatment, and at the EOT and TOC visits:

1. Fever* (> 38.5 °C)
2. Hypothermia
3. Tachypnea corresponding to
   Age 3 months to < 1 year: > 50 breaths per minute
   Age 1 year to < 5 years: > 40 breaths per minute
   Age ≥ 5 Years: > 20 breaths per minute
4. Dyspnoea
5. Retractions (suprasternal, intercostal or subcostal)
6. Grunting
7. Nasal flaring
8. Apnoea
9. Altered mental status
10. Hypoxemia (pulse oximetry measurement ≤ 92% on room air)

At Day 4, and EOT assessments, the Blinded Investigator must also rate the clinical outcome of pneumonia compared to baseline, as:

- ***Cured:*** no signs or symptoms of pneumonia are detectable
- ***Improved:*** clinically relevant improvement in overall signs and symptoms
- ***Unchanged:*** no change from baseline, or minor change not judged to be clinically relevant
- ***Worsened:*** clinically relevant increase in the overall severity of signs and symptoms

The date of discharge from hospital must be recorded in the CRF.

* Body temperature may be axillary, oral, rectal, tympanic or by skin temperature (e.g., by a patch); however, for each patient, only one method should be used consistently throughout the study.

5.3.2 Clinical outcome of therapy

At the TOC visit, the Blinded Investigator must rate the overall clinical outcome as:

- ***Clinical cure***: signs and symptoms of pneumonia normalized or improved to an extent that further antibiotic therapy is not necessary, stabilization or improvement of chest X-rays post-baseline if these are available
- ***Clinical failure***: persistence of clinically relevant signs and symptoms of pneumonia, and a need for continued or additional antibiotics (including macrolides) to treat respiratory illness
- ***Clinically unevaluable***: unable to examine the patient or to determine disease status within 7 to 14 days after EOT

At the LFU visit (see Section 5.2.7), the Blinded Investigator must assess relapse in patients with a TOC clinical outcome of 'clinical cure' as follows:

- ***Clinical cure maintained***: no further antimicrobial therapy was necessary for treatment of the infection.
- ***Clinical relapse***: signs and symptoms of CAP or HAP (see Section 5.3.1) reappeared such that additional antimicrobial therapy was necessary.
- ***Clinically unevaluable***: absence of clinical assessments at LFU, or concomitant treatment with a systemic antibiotic active against Gram-positive or Gram-negative bacteria, administered for a reason other than the CAP or HAP.

At the LFU assessment, the TOC clinical outcomes of 'clinical failure' or 'clinically unevaluable' will be carried forward to the LFU outcome assessment.

5.3.3 Microbiological outcome of therapy

The microbiological outcome of therapy is to be based on the results from microbiological cultures at the EOT and TOC visits, as follows:

- ***Microbiological eradication***: causative pathogen isolated at baseline is no longer detected in valid samples obtained.
- ***Presumed microbiological eradication***: causative pathogen isolated at baseline, but no valid sample obtained or required post-therapy because of clinical improvement (clinical outcome of cure).
- ***Microbiological persistence***: same causative pathogen isolated at baseline and in valid samples obtained at EOT and/or TOC.
- ***Superinfection***: different pathogens, potentially causative, isolated at baseline and in valid samples obtained at EOT and/or TOC, or a new potentially causative pathogen isolated at EOT or TOC in the absence of an isolated pre-treatment pathogen.
- ***Microbiologically non-evaluable***: no causative pathogen isolated at baseline, or unable to obtain valid sample at EOT or TOC in cases of clinical failure or in clinically unevaluable patients.

At the LFU visit, (see Section 5.2.7), the Blinded Investigator must assess relapse in patients with a TOC assessment of 'microbiological eradication' or 'presumed microbiological eradication' as follows:

- ***Microbiological eradication maintained***: microbiological eradication at the TOC visit and no growth at the LFU visit of a potential pathogen from a valid culture taken at the original site of infection.
- ***Presumed microbiological eradication maintained***: microbiological eradication or presumed microbiological eradication at the TOC visit and no growth at the LFU visit of a potential pathogen from any valid culture taken at the original site of infection, and no clinical relapse.
- ***Microbiological relapse***: growth of the original pathogen at the original site of infection, with or without the presence of clinical signs or symptoms of infection.
- ***Presumed microbiological relapse***: no growth of a potential pathogen from any valid culture taken at the original site of infection, in the presence of clinical signs or symptoms of infection
- ***Superinfection***: different potentially causative pathogens isolated at baseline and in valid samples obtained at the LFU visit, or a new potentially causative pathogen isolated at the LFU visit in the absence of a pathogen isolated at baseline.
- ***Microbiologically non-evaluable***: no pathogen isolated at baseline, or absence of clinical determination at TOC, or 'Other' (specified by the Blinded Investigator).

At the LFU assessment, (see Section 5.2.7), TOC microbiological outcomes of 'microbiological persistence', 'superinfection' or 'microbiologically non-evaluable' will be carried forward to the LFU outcome assessment.

5.4 Microbiology assessments

Blood samples for culture and Gram stain are to be obtained at Screening if feasible. Post-baseline blood cultures should be obtained as clinically indicated according to local practice during therapy, at EOT, and at the TOC visit. At the LFU visit, sampling is only to be undertaken if considered necessary by the Blinded Investigator to evaluate microbiological relapse (need for further antibiotic treatment).

Sputum samples for culture and Gram stain are to be obtained at Screening, at EOT, and at the TOC and LFU visits for patients able to produce sputum. The numbers of white blood cells and epithelial cells in each sputum sample must be recorded (for details, see the Microbiology Manual).

Tracheal aspirates or broncho-alveolar lavage samples for culture and Gram stain may be used if obtained in patients requiring mechanical ventilation or who undergo bronchoscopy that is clinically indicated.

Potential pathogens from any culture are to be stored and shipped to a central laboratory. The Microbiology Manual describes the procedures for collection, culture, susceptibility testing, storage, and shipping of microbiology samples.

5.5 Pharmacokinetics assessments

5.5.1 Collection and preparation of plasma samples

Blood samples of 200 to 300 µL are to be obtained for PK analysis from at least 15 patients in each of the two age categories of < 6 years and ≥ 6 years on Day 3 at the following time points:

- Children aged 2 years and older: pre-dose, and at 2h (end of infusion), 4h, 6h, and 8h after start of infusion
- Children aged less than 2 years: pre-dose and at 4h (end of infusion), 6h, and 8h after start of infusion

Blood sampling should be performed after the daily visit of the Blinded Investigator in order to maintain the blind. The date and exact times of blood sampling must be recorded in the CRF.

Blood for PK analysis should be collected by heel prick or fingertip prick or by regular venous puncture or through an existing arterial line, depending on age and according to local practice.

Blood must be collected in pre-chilled tubes containing EDTA as an anticoagulant, and containing citric acid. Samples must be centrifuged, and the supernatant frozen. Samples must be stored and shipped to as described in the Pharmacokinetics Manual.

5.5.2 Analysis of ceftobiprole concentrations

Plasma will be analysed for concentrations of ceftobiprole, and if applicable for concentrations of ceftobiprole medocaril and the open-ring metabolite (BAL1029). The analysis must be performed using validated gradient reversed-phase liquid chromatography coupled with a tandem mass spectrometer (LC/LC-MS/MS); analysis will be carried out under the supervision of the Sponsor.

Calibration and quality control (QC) samples must be prepared in blank and pre-tested human plasma, and will be subject to the same assay procedure as experimental samples. The limit of quantification is to be defined as the lowest concentration of analyte in a human plasma sample, which can be quantitatively determined with inter-assay precision and accuracy of 100 ± 20%. Lower found concentrations must be denoted as 'BLQ' (below limit of quantitation). Assay performance will be controlled by the analysis of QC samples. When calculating mean drug levels for a patient cohort, if < 50% of samples are BLQ, drug levels in these samples will be set to zero. If ≥ 50% of samples are BLQ, no mean value will be calculated.

5.5.3 Pharmacokinetic parameters

Concentrations of ceftobiprole, ceftobiprole medocaril, and metabolite in plasma will be determined; these results will be analysed by use of descriptive statistics.

5.6 Safety assessments

The Blinded Investigator must evaluate patient safety by monitoring and recording all AEs and serious adverse events (SAEs), physical examination, vital signs, and laboratory tests (see Table 4). Safety assessments must be performed at intervals indicated in the Schedule of Assessments (see Table 4). More frequent assessments may be performed at the Blinded Investigator's discretion, if medically indicated.

5.6.1 Adverse events

See Section 7 for details regarding AE collection and management.

5.6.2 Safety laboratory tests

Blood and urine samples obtained at screening and on Day 4, EOT and the TOC visit must be analyzed for the following laboratory parameters:

Haematology: Haemoglobin concentration, haematocrit, red blood cell (RBC) count, total and differential white blood cell (WBC) count, platelet count, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), reticulocyte count.

In children aged 6 years and older, and in younger patients not treated with vancomycin, additionally direct antiglobulin (Coombs) test at screening and TOC.

Blood chemistry: C-reactive protein, creatinine, alanine amino transferase (ALT), aspartate aminotransferase (AST), total bilirubin, sodium, potassium. In children aged 6 years and older, and in younger patients not treated with vancomycin, additionally haptoglobin at screening, Day 4, and EOT.

Urinalysis: Dipstick for pH, glucose*, blood*, and protein*
(*microscopic examination of sediment if positive/strong positive)

Blood draws should be performed according to standard procedures of the institution. The choice of site and procedure for blood draws (e.g., heel prick, fingertip prick, venous site, or through an indwelling venous or arterial catheter) is to be made by the Blinded Investigator. The patient's age, the accessibility of the puncture site, and the blood volume required, should all be taken into consideration when selecting the puncture site and method. Maximum blood volumes for laboratory testing per visit and over the course of the study need to be considered.

Children with bodyweight ≤ 15 kg (approximately 3–4 years and younger) should always be treated with blood-saving methods and small tubes.

Creatinine clearance is estimated using the Schwartz Estimate.

The anticipated blood volume required for safety laboratory and PK assessment using regular tubes (S-Monovette®) and technique is:

	Haematology (mL)	Biochemistry (mL)	Haptoglobin and Coombs (mL)	PK (mL)	Total (mL)
Screening	2.6	2.6	5.2		10.4
Day 3				1.5	1.5
Day 4	2.6	2.6	2.6		7.8
EOT	2.6	2.6	2.6		7.8
TOC	2.6	2.6	2.6		7.8
Total	**10.4**	**10.4**	**13**	**1.5**	**35.3**

The anticipated blood volume required for safety laboratory and PK assessment using micro sampling technique and small tubes (Microvette®) is:

	Haematology (mL)	Biochemistry (mL)	Haptoglobin and Coombs (mL)	PK (mL)	Total (mL)
Screening	0.5	0.5	1.1		2.1
Day 3				1.5	1.5
Day 4	0.5	0.5	0.6		1.6
EOT	0.5	0.5	0.6		1.6
TOC	0.5	0.5	0.5		1.5
Total	**2.0**	**2.0**	**2.8**	**1.5**	**8.3**

Total circulating blood volume and maximal blood volume for laboratory testing based on body weight:

	Total circulating blood volume (mL)	Maximum total blood volume for testing (mL)	Maximum per visit blood volume for testing (mL)
5 kg	400	12	4
10 kg	800	24	8
15 kg	1200	36	12
20 kg	1600	48	16

In the event of unexplained abnormal laboratory test values, the tests should be repeated if medically indicated, and followed-up until return to the normal range, stabilization, and/or until an adequate explanation of the abnormality has been determined. When a clear explanation is established this must be recorded in the CRF. Abnormal laboratory results should not be recorded as an AE unless the abnormality is associated with a clinically relevant condition (see Section 7.3.2.1.1).

5.6.3 Vital signs

Vital signs (including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) must be recorded at Screening, prior to first administration of study drug and thereafter every 8 hours during the active study drug treatment period, and at the EOT and TOC clinical assessments. Weight will be assessed at Screening, and the EOT visit. Height will be assessed only at Screening.

Body temperature may be axillary, oral, rectal, tympanic or skin. However, for each patient, only one method should be used consistently throughout the study.

Any clinically significant change in vital signs, or worsening of, a patient's condition that occurs after first study-drug administration must be reported as an AE (see Section 7.1.2).

5.6.4 Oxygen saturation by pulse oximetry

Pulse oximetry measurements must be performed together with the assessment of vital signs, at Screening, before administration of the first dose of study drug and every 8 hours thereafter during the active study drug treatment period, and at the time of EOT and TOC assessments (see Table 4). Results of each assessment (as % oxygen saturation) must be recorded in the CRF.

5.6.5 Physical examination

Each patient must undergo a physical examination at Screening, at Day 4 and at the EOT visit. Abnormalities are to be described in the CRF.

Any clinically-significant physical change in, or worsening of, a patient's condition that occurs after first study-drug administration must be reported as an AE (see Section 7.1.2).

6 STUDY DRUGS

6.1 Dose and schedule

The intended doses and the schedule of ceftobiprole medocaril and comparator cephalosporin antibiotics (ceftazidime or ceftriaxone) may not be modified. Patients requiring dose modifications of these antibiotics for safety reasons should be withdrawn from the study.

Vancomycin doses should be modified for patients with renal impairment, and to maintain recommended levels of drug exposure (see Section 6.1.2.3).

On each treatment day, study-drug administration should occur within ±1 h from the scheduled time point for ≤ q6h dose regimens, and ±2 h from the scheduled time point for > q6h dose regimens.

6.1.1 Ceftobiprole medocaril

Patients are to receive IV infusions of ceftobiprole (given as ceftobiprole medocaril) q8h at age-adjusted doses and infusion durations as follows:

- 3 months to < 2 years: 20 mg/kg as 4-hour infusions
- 2 years to < 6 years: 20 mg/kg as 2-hour infusions
- 6 years to < 12 years: 15 mg/kg as 2-hour infusions
- 12 years to < 18 years: 10 mg/kg as 2-hour infusions

Note: the maximum dose, regardless of body weight, is 500 mg ceftobiprole q8h (maximum total daily dose of 1500 mg ceftobiprole).

To limit the infusion volume for patients < 12 years of age, ceftobiprole medocaril is to be administered at a concentration of 4 mg/mL ceftobiprole using dextrose 5% as carrier solution (see Section 6.2.1).

For patients aged 12 years to < 18 years, ceftobiprole medocaril is to be administered at a concentration of 2 mg/mL ceftobiprole, which reflects the use in adults.

Criteria that permit a switch from IV to oral antibiotics therapy, and the recommended oral antibiotics, are described in Section 3.4.

Treatment of suspected infections by *P. aeruginosa* may be added at the discretion of the Blinded Investigator, in accordance with local practice (Section 3.6.2). Patients requiring concomitant treatment with a macrolide should be considered as clinical failures and withdrawn from study treatment, as described in Section 4.4.

6.1.2 Comparators

6.1.2.1 Standard-of-care comparator for CAP

The standard-of-care comparator antibiotic treatment is IV ceftriaxone 50–80 mg/kg administered once daily up to a maximum dose of 2 g/day. The actual dose of ceftriaxone within a dose range of 50 to 80 mg/kg (maximum dose of 2 g/d) is to be determined by the Blinded Investigator prior to first study drug administration. The dose administered on Day 1 should be not be modified throughout subsequent study days. Ceftriaxone is to be administered at a concentration of 20 mg/mL in all age groups.

Optional:

- Patients should receive vancomycin at a recommended dose of 10–15 mg/kg every 6 hours (40 to 60 mg/kg per day) as an IV infusion, in addition to IV standard-of-care cephalosporin (comparator) antibiotic treatment when MRSA is suspected or confirmed, or at the discretion of the Blinded Investigator. Vancomycin serum concentrations should be monitored in all patients receiving vancomycin and the dosage adjusted as needed in order to maintain serum concentrations within the therapeutic window (see Section 6.1.2.3). Vancomycin dosage in patients with impaired renal function should be modified in accordance with the approved product

label. The adjustment of vancomycin dose levels will be performed by the unblinded investigators. Vancomycin is to be administered at a concentration of 4 mg/mL in all age groups.

- Anti-pseudomonal treatment is described in Section 3.6.2.

Withdrawal of patients requiring treatment with a macrolide is described in Section 4.4.

Criteria that permit a switch from IV to oral antibiotics therapy, and the recommended oral antibiotics, are described in Section 3.4.

6.1.2.2 Standard-of-care comparator for HAP

The standard-of-care comparator antibiotic treatment is IV ceftazidime 50 mg/kg administered every 8 hours up to a maximum of 6 g/day.

Optional:

- All patients should receive vancomycin at a recommended dose of 10–15 mg/kg q6h (40–60 mg/kg per day) as an IV infusion, in addition to IV ceftazidime when MRSA is suspected or confirmed, or at the discretion of the Blinded Investigator. Vancomycin serum concentrations should be monitored in all patients receiving vancomycin and the dosage adjusted as needed in order to maintain serum concentrations within the therapeutic window (see Section 6.1.2.3). Vancomycin dosage in patients with impaired renal function should be modified in accordance with the approved product label. The adjustment of vancomycin dose levels will be performed by the unblinded investigators. Vancomycin is to be administered at a concentration of 4 mg/mL for all age groups.

  In the event of scheduling conflicts, the order of administration should always be ceftazidime, followed by vancomycin.

  Vancomycin must not be given together with ceftazidime in the same line; the line must be flushed when vancomycin is given directly after ceftazidime.

- Anti-pseudomonal treatment is described in Section 3.6.2.

Withdrawal of patients requiring treatment with a macrolide is described in Section 4.4.

Criteria that permit a switch from IV to oral antibiotics therapy, and the recommended oral antibiotics, are described in Section 3.4.

6.1.2.3 Monitoring of vancomycin serum concentrations

The serum concentration of vancomycin should be monitored at the second day of treatment immediately prior to the next dose (trough level). Therapeutic steady-state trough vancomycin blood levels should be maintained at 15–20 mg/L.

The concentrations should normally be monitored two or three times per week.

The adjustment of vancomycin dose levels is to be performed by the unblinded investigators.

6.2 Administration

The highest total infusion volume in this study occurs in HAP patients treated with ceftazidime and vancomycin. This highest possible infusion volume remains in all instances below the maintenance need for water in parenteral fluid therapy calculated by the Holliday-Segar formula (see Table 5) (Holliday 1957).

Table 5 Total Infusion volumes in HAP patients treated with ceftazidime and vancomycin and maintenance fluid volumes

Age group	Body weight (kg)*	Infusion volume (mL)	Maintenance fluid volume (mL)**
3 months to < 2 years	5–12	113–270	500–1100
2 years to < 6 years	10–28	225–630	1000–1660
6 years to < 12 years	16–62	360–800	1300–2340
12 years to < 18 years	30–92	675–800	1700–2940

* Range from the 5th percentile for the lowest age up to the 95th percentile of the highest age.

** 100 mL/kg for the first 10 kg body weight, 50 mL/kg for the second 10 kg body weight, and 20 mL/kg for the remaining body weight.

6.2.1 Ceftobiprole medocaril

Details on study drug preparation and administration are provided in the Pharmacy Manual. Procedures can be briefly summarized as follows:

Ceftobiprole medocaril is to be administered intravenously, depending on age, as follows

- **3 months to < 12 years:** ceftobiprole medocaril administered at a concentration of 4 mg/mL ceftobiprole using dextrose 5% as carrier solution
- **12 years to < 18 years:** ceftobiprole medocaril administered at a concentration of 2 mg/mL ceftobiprole using either physiological saline (NaCl 0.9%) or dextrose 5% as carrier solution

Ceftobiprole medocaril will be supplied in vials containing 500 mg ceftobiprole (corresponding to 667 mg of ceftobiprole medocaril) as lyophilized powder and must be reconstituted and diluted as shown in Table 6.

Table 6 Reconstitution and dilution of ceftobiprole

	Age Group 3 months to < 12 years	Age Group 12 years to < 18 years
Step 1: Reconstitution	10 mL dextrose 5% Concentration of the reconstituted solution: 50 mg/mL ceftobiprole. Stability of the reconstituted solution: • 1 hour at room temperature • Up to 24 hours in a refrigerator at 2 °C to 8 °C	10 mL dextrose 5% Concentration of the reconstituted solution: 50 mg/mL ceftobiprole. Stability of the reconstituted solution: • 1 hour at room temperature • Up to 24 hours in a refrigerator at 2 °C to 8 °C
Step 2: Dilution	Dextrose 5% to achieve a ceftobiprole concentration of 4 mg/mL in the final solution for infusion. Stability of the solution for infusion: 24 hours at 2 °C to 8 °C plus 12 hours at room temperature, including the infusion into the patient. Note: Reconstitution, dilution and infusion including an up to 4-hour infusion period must be completed within 24 hours. Only dextrose 5% is permitted for reconstitution and dilution.	Either physiological saline (NaCl 0.9%) or dextrose 5% to achieve a ceftobiprole concentration of 2 mg/mL in the final solution for infusion Stability of the solution for infusion: 8 hours at room temperature 96 hours in a refrigerator at 2 °C to 8 °C

Reconstituted and infusion solutions should be prepared under sterile conditions. Unless the method of reconstitution/dilution precludes the risk of microbiological contamination, the solutions should be used immediately, rather than within the times based on chemical and physical stability.

The reconstituted and infusion solutions should not be frozen, and should not be exposed to direct sunlight before infusion.

If the infusion solution is stored in the refrigerator, it should be equilibrated to room temperature prior to administration. The infusion solution does not need to be protected from light during administration.

Further details of study drug administration are described in the Pharmacy Manual.

6.2.2 Comparator antibiotics

Comparator antibiotics must be administered according to the manufacturers' instructions, and as described in Section 6.1.2.

6.3 Blinding and randomization

This is an investigator-blind study.

There is to be at least one Blinded Investigator at each centre who does not know the patient's assigned treatment. This blinded observer is to conduct the clinical assessments,

including with reference to the criteria for switching to oral study drug. The assessments are to be made in the patient ward when no study drugs are being administered. The remaining investigators, study team, patients, their parents, and the pharmacy staff, are unblinded. A Blinding Management Plan must be established at each centre.

Patients are to be randomized with stratification by diagnosis of HAP or CAP and age as described in Section 3.1. Within each group, patients are to be randomized 2:1 to receive ceftobiprole or comparator antibiotics ceftazidime ± vancomycin (for HAP) or ceftriaxone ± vancomycin (for CAP). Randomization will be carried out using a central Interactive Voice Response System (IVRS) and/or Interactive Web-based Response System (IWRS) based on a computer-generated randomization schedule prepared by the Sponsor before the study.

The following personnel will have access to the randomization list and the identity of the study drugs.

- those responsible for labelling, packaging, and respective documentation
- those performing PK analyses
- those setting up the random scheme and IVRS/IWRS
- the unblinded centre study team, including unblinded investigators at each centre
- the unblinded pharmacist or delegate responsible for blinded study-drug preparation and documentation
- those required to break the blind for expedited reporting purposes to health authorities and other relevant institutions
- those responsible for clinical monitoring (unblinded Monitor) and his/ her supervisor (unblinded monitoring report review)
- the unblinded data manager responsible for cleaning unblinded infusion and PK data
- the unblinded statistician, if required for safety reasons, producing the interim analysis and Data and Safety Monitoring Board (DSMB) outputs

These personnel must not disclose any details of the randomization scheme or the treatment code of study drugs.

6.4 Unblinding methods

Individual treatment codes for each randomized patient will be available to Blinded Investigators from the IVRS/IWRS system. The Blinded Investigator is responsible for monitoring and recording AEs.

The treatment code should only be broken in medical emergencies; it is advisable to contact the medical monitor prior to breaking the blind. The Blinded Investigator must record the reason for unblinding in the patient's records/source documents.

In order to maintain the investigator-blinded nature of the study, the allocation of the investigational product(s) for the patient must not be communicated further, unless required for the treatment and/or surveillance of the patient. Adverse events and SAEs must be reported as outlined in Section 7. Serious adverse event reporting is to be performed by the Blinded Investigator to prevent accidental unblinding of the

Sponsor/designee. The Sponsor/designee might break the blind via IVRS/IWRS for regulatory reporting purposes. This must be fully documented, and only the minimum number of staff necessary are to have access to the unblinded information.

Detailed handling instructions are provided in the IVRS/IWRS Manual.

Systematic unblinding of the clinical database will occur after database lock as described in the Data Management Plan and Statistical Analysis Plan (SAP).

6.5 Drug accountability and compliance check

Compliance will be assessed by direct observation of each patient during infusion of the study medication, and by measurement of ceftobiprole concentrations in plasma.

A Drug Dispensing Log must be kept current and should contain the following information for ceftobiprole, ceftriaxone, ceftazidime, and vancomycin:

- The identification of the patient to whom the drug was dispensed
- The date(s), time and quantity of the drug dispensed to the patient
- The initials of the person who dispensed the drug

The inventory must be available for inspection by the unblinded clinical monitor. Drug supplies, including partially used or empty containers and the dispensing logs, must be maintained for verification by the unblinded clinical monitor.

When requested in writing by Basilea, unused drug supplies may be destroyed by the unblinded investigator. Records shall be maintained by the unblinded investigator of any such alternate disposition of the test drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the test substance. Such records shall be submitted to Basilea.

6.6 Packaging and labelling

Study drug vials (including ceftobiprole, ceftriaxone, ceftazidime, and vancomycin,) will be supplied by Basilea to the unblinded investigator or to the Unblinded Pharmacist. Basilea will ensure that the study medication and certificates of analysis are available before the start of the study.

Study drug for IV administration will be presented as vials of sterile lyophilized ceftobiprole medocaril (BAL5788) containing the equivalent of 500 mg ceftobiprole which will be reconstituted and diluted as described in Section 6.2.1. The lyophilisate will be stored in a refrigerator (2°C to 8°C).

The study drug vial labels will identify, e.g., the Sponsor, study number, vial contents, batch number and expiry date as per applicable guidelines.

Study drug must be kept in a secure location under adequate storage conditions. Further details on handling, preparation, and administration of IV ceftobiprole are described in the Pharmacy Manual.

7 PATIENT SAFETY

7.1 Definitions

7.1.1 Adverse occurrence

An adverse occurrence is any untoward medical occurrence taking place after informed consent and before first study-drug administration.

7.1.2 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

7.1.2.1 Treatment-emergent adverse event

A treatment-emergent adverse event is any AE which occurs from the start of first dosing up to and including the scheduled LFU visit.

7.1.3 Serious adverse event

A serious adverse event (SAE) is any AE that meets one or more of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient, or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, and development of drug dependency or drug abuse.

It should be noted that:

- Death is considered an outcome of an AE. Whenever possible the underlying cause of death must be reported as the AE.
- A life-threatening SAE is any adverse experience that places the patient at risk of death at the time of its occurrence, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalisation is defined as any inpatient admission, even if for less than 24 hours. For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from a medical floor to the coronary care unit, or from the neurological floor to the tuberculosis unit).

The following hospitalisations, whether planned before or during the study, should not be considered SAEs:

- Routine treatment or monitoring of the HAP or CAP, not associated with any deterioration in condition (e.g., hospitalisations related to study procedures, such as study-drug administration, PK assessments, etc).
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the HAP or CAP and has not worsened.
- Admission to a hospital or other institution for general care, not associated with any deterioration in condition.
- Treatment on an emergency outpatient basis for an event which does not meet any of the above definitions of 'serious', and does not result in hospital admission.

7.1.3.1 Suspected unexpected serious adverse reaction

A suspected unexpected serious adverse reaction (SUSAR) is any SAE considered to be related to the study treatment and for which the nature or severity is not consistent with the applicable reference safety information (i.e., regardless of whether the nature or severity of an SAE has been previously observed/documented).

Note: Expectedness of SAEs will be assessed by the Sponsor against the applicable reference safety information.

7.2 Evaluation of adverse events

7.2.1 Severity

The intensity of an AE will be graded on the following three-point scale:

- Mild: discomfort but no disruption of normal daily activity
- Moderate: discomfort sufficient to reduce or affect daily activity
- Severe: inability to work or to perform normal daily activities

7.2.2 Relationship

The relationship of AEs to the study treatment must be assessed by the Blinded Investigator as one of the following:

- not related
- unlikely
- possible
- probable

Appendix 2 provides criteria for relationship assessments.

According to the Sponsor's criteria for causality assessment, a causal relationship will be suspected for all AEs reported with a relationship of 'possible' or 'probable', and those with missing or unknown relationships.

7.3 Handling of safety information and collection periods

7.3.1 Handling of safety data during the pre-treatment period

Any relevant change in, or worsening of, a patient's condition occurring after consent, but prior to the start of first study-drug administration, must be recorded in the CRF as pre-dose medical history.

If a change in, or worsening of, a patient's condition is considered to be serious (i.e., meets one or more of the criteria for an SAE in Section 7.1.3), this information must also be reported to the Sponsor's safety representative, using the same forms and procedures as for an SAE (see Section 7.3.2.2).

7.3.2 Handling of safety data during the treatment period and up to the last scheduled follow-up

From the start of first dosing up to and including the LFU visit, any change in, or worsening of, the patient's condition must be collected and reported in the CRF as an AE (see Section 7.3.2.1). Serious adverse events must be additionally reported and recorded on SAE report forms (see Section 7.3.2.2).

7.3.2.1 Adverse event management

The Blinded Investigator or the physician in attendance should administer therapy as clinically indicated for any AE/SAE that occurs.

7.3.2.1.1 Data collection

All AEs directly observed (physical examination, laboratory test, or other assessments), mentioned by the patient, or reported by the patient upon non-directive questioning, must be recorded on the AE pages of the CRF.

The Blinded Investigator should consider reports from the parents, LARs or caregivers when recording AEs.

All AEs must be recorded in the English language in the CRF and should include the following information:

1. Term. If possible, a diagnosis should be documented rather than signs and symptoms, using self-explanatory and concise medical terminology.

   Note: Use of the AE term 'disease progression'/'lack of efficacy', or equivalent terms, should be avoided. Instead, a diagnosis, signs, or symptoms should be used to describe the worsening of the HAP or CAP.
2. Duration (start and end dates).
3. Severity grade (three-point scale, see Section 7.2.1).
4. Relationship to study treatment (see Section 7.2.2 and Appendix 2).
5. Action(s) taken with regards to the study treatment or additional treatments given for the event.
6. Whether the event is an SAE (see Section 7.1.3).
7. Outcome.

Abnormal laboratory results should not be recorded as an AE unless the abnormal result meets one or more of the following criteria:

- induces clinical signs or symptoms which require therapy or additional diagnostic evaluation
- requires changes in study drug dosing or discontinuation of study participation
- is considered clinically significant

Signs, symptoms or diagnosis associated with these abnormal results must be recorded on the AEs page of the CRF.

Adverse events must also be reported in the source document with at least the nature of the event, the start and end date, the relationship to the study drug, and the treatment (if applicable).

7.3.2.1.2 Follow-up

Once an AE is detected, it must be proactively followed 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.

All AEs must be followed-up until they have returned to baseline status or have stabilised, or until the scheduled LFU visit.

In addition, an AE which remains unresolved after completion of the study (including the scheduled LFU visit) and meets one or more of the criteria listed below, requires detailed evaluation, follow-up and, if necessary, specific medical treatment until the AE is resolved or a reasonable explanation for its persistence is found:

- an AE evaluated as related to the study drug
- an AE that led to a patient withdrawal from the study
- an SAE

These cases must be followed-up on the CRF unless otherwise agreed with the Sponsor.

7.3.2.2 Serious adverse event recording and reporting

In addition to being reported and followed-up as AEs (see Section 7.3.2.1), SAEs must be reported to the Sponsor's safety representative listed below, within 24 hours of awareness of the event.

The Blinded Investigator must complete the 'Serious Adverse Event Report Form' in English, and send the completed, signed form by fax or email to:

PrimeVigilance Limited
The Surrey Research Park
26–28 Frederick Sanger Road
Guildford, Surrey GU2 7YD, UK
Email: Basilea@primevigilance.com
eFax (UK): +44 (0)800 0669192

Such preliminary reports must be followed by detailed anonymised descriptions, which may include copies of hospital case reports, autopsy reports, and other documents if requested and applicable.

The original SAE Report Form and the correspondence to the Sponsor reporting the SAE (fax confirmation sheet/email) must be kept at the study centre in the Investigator Site File (ISF).

7.3.3 Handling of post-study safety data

Any AE occurring after the LFU visit which is considered to be both:

- serious (i.e., meets one or more of the criteria listed for SAEs, see Section 7.1.3), and
- related to the study drug (see Section 7.2.2 and Appendix 2)

should be reported to the Sponsor's designated safety representative using the same forms and procedures as for an SAE (see Section 7.3.2.2).

Events occurring after the LFU visit should not be reported in the CRF.

7.3.4 Reporting of SAEs to regulatory authorities

7.3.4.1 Sponsor's responsibilities

The Sponsor's safety representative must ensure the reporting of SUSARs and any expeditable SAEs to regulatory Authorities in accordance with applicable law.

In the event of a SUSAR, the Sponsor will ensure that all investigators involved in all studies with ceftobiprole medocaril are informed.

7.3.4.2 Investigator's responsibilities

The Blinded Investigator is responsible for informing the local Independent Ethics Committee / Institutional Review Board (IEC/IRB), and any other applicable bodies, of SUSARs and any other expeditable SAEs, in accordance with applicable laws. This activity may be delegated.

7.4 Pregnancy

7.4.1 Contraception for women of childbearing potential

There are no adequate and well-controlled studies with ceftobiprole in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or post-natal development. As no data in exposed human pregnancies are available, ceftobiprole should not be used during pregnancy.

The Blinded Investigator must make every effort to ensure that a clinical study patient does not become pregnant during the study. This should be done, and documented, as part of the consent process, by explaining clearly to the patient the potential dangers of becoming pregnant, and providing each patient with information about appropriate medically-approved effective contraception (see below).

Pregnancy testing must be conducted on all menarcheal female patients prior to administration of the first dose of study drug. If results of the pregnancy test are positive, the patient must not be enrolled in the study.

Female patients of childbearing potential who enrol in this study must agree (in consultation with their parents and doctors, as applicable) to use a highly reliable method of contraception during the study. Such methods may include:

- Intrauterine device (IUD)
- Combined (oestrogen- and progesterone-containing) hormonal contraception (oral, vaginal ring or transdermal patch) with an ethinylestradiol dose of at least 30 µg, plus use of male condoms (preferably with spermicides), female condoms, a female diaphragm or a cervical cap
- Total sexual abstinence

7.4.2 Reporting and handling of pregnancies

Female patients must inform the Blinded Investigator within 24 hours if they have any concerns about possible reduction of contraceptive effectivity (e.g., forgotten pill or vomiting) during the study. In these cases the patients must return to the study centre as soon as possible, but not later than 24 hours, after the Blinded Investigator is informed.

Female patients must inform the Blinded Investigator if they become pregnant during the study. The study drug must be discontinued immediately when a patient becomes pregnant. The patient must be monitored until conclusion of the pregnancy and infants must be followed-up at least for 8 weeks after delivery.

The Blinded Investigator must immediately notify the Sponsor's safety representative about any pregnancy by submitting a Pregnancy Report Form, in accordance with the requirements (timelines and contact details) of an SAE (see Section 7.3.2.2). In addition, pregnancy-related adverse outcomes must also be reported as AEs or SAEs (see Section 7.3.2). Note that an induced abortion which is not required by an AE does not constitute an SAE.

The Blinded Investigator must notify the local IEC/IRB about any pregnancies resulting in an adverse outcome, in accordance with applicable laws and regulations.

7.5 Data and Safety Monitoring Board

The composition, roles and responsibilities of the DSMB are described in a separate DSMB Charter. Briefly, members of the DSMB will review patient data for periodic scheduled data review meetings.

An interim analysis of safety data will be performed by the DSMB after randomization of approximately 50 patients. The Blinded Investigator will remain blinded to the assigned treatment during this analysis (see Section 8.8).

8 STATISTICAL CONSIDERATIONS

8.1 Sample size justification

The randomization of 138 patients is expected to give at least 125 evaluable patients (at least 92 receiving ceftobiprole and at least 46 receiving the comparator, assuming approximately a 10% dropout rate from randomization to the EOT and TOC visits).

At least 50 patients are planned to be enrolled in 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).

Treatment of 92 patients (safety population) with ceftobiprole will yield a > 95% probability of observing at least one AE type if the actual probability of this event is > 3.2%.

In an age-related analysis, if at least 33 patients receiving ceftobiprole are aged < 6 years and at least 33 are aged ≥ 6 years, this will yield a 95% probability of observing at least one AE type in each of the two age groups if the actual probability of this event is > 8.7%.

At least 33 patients on ceftobiprole and at least 17 patients on IV standard-of-care cephalosporin treatment must be included in the age categories < 6 years (Groups 1, 2, 5 and 6) and ≥ 6 years (Groups 3, 4, 7 and 8; see Section 8.3).

8.2 Analysis populations

The analysis populations are defined as follows:

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 (9 infusions) of study drug, had a valid clinical outcome assessment at TOC, no major protocol violations, and no systemic non-study antibiotic therapy.

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 by the appropriate methodology.

8.3 General statistical considerations

Study results will be presented by infection type, and if applicable by age group within each infection type, as follows:

- Group 1: Patients aged 3 months to < 2 years with CAP
- Group 2: Patients aged 2 years to < 6 years with CAP
- Group 3: Patients aged 6 years to < 12 years with CAP
- Group 4: Patients aged 12 years to < 18 years with CAP
- Group 5: Patients aged 3 months to < 2 years with HAP
- Group 6: Patients aged 2 years to < 6 years with HAP
- Group 7: Patients aged 6 years to < 12 years with HAP
- Group 8: Patients aged 12 years to < 18 years with HAP

No formal hypothesis testing will be performed. Descriptive statistics will be applied to the primary variable, with frequency tables used to characterise the safety profile of ceftobiprole, and the numbers of patients with adverse changes in laboratory test results, vital signs, and physical examination results.

The secondary variable of clinical cure will be compared between ceftobiprole and the standard-of-care comparator IV antibiotic treatment. The between-group difference, along with the respective 95% CI, will be displayed at the study time points Day 4, EOT, and TOC.

8.4 Presentation of clinical results

Presence of disease signs and symptoms at baseline, changes in disease signs and symptoms and in overall clinical status, clinical outcomes at TOC, microbiological outcomes at TOC, and findings at the LFU visit will be presented in individual patient listings, and summarized by descriptive statistics.

8.5 Analyses of endpoints

The primary endpoint of the study (see Section 3.2.1) is analysis of AEs assessed on each of the first 3 days of study-drug treatment, and at the EOT, TOC, and LFU visits (Safety population). Other timepoints may also be analysed.

The secondary endpoints (see Section 3.2.2) are:

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).

Clinical cure rates at TOC (see Section 5.3.2) in all patients (HAP and CAP alone and/or combined) will be tabulated for ceftobiprole and the comparators, and the between-group difference will be displayed along with the respective 95% CI.

The between-group difference in clinical cure rates at TOC will be displayed, along with the respective 95% CI. The between-group difference in the percentages of patients rated as improved or cured regarding their clinical signs and symptoms at study Day 4 and EOT (see Section 5.3) will be also be displayed, along with the respective 95% CI.

Changes from baseline in signs and symptoms and in overall clinical status (see Section 5.3.1) will be analysed by descriptive statistics. Duration of hospitalisation, defined as the time from start of study drug therapy to discharge, will be analysed by descriptive statistics and by a time to event analysis.

A full Statistical Analysis Plan (SAP) will be prepared before database lock.

8.6 Safety analyses

The incidence of AEs will be displayed by MedDRA System Organ Class and Preferred Term. In addition, listings will be provided by individual patient. Vital signs will be listed and summarised by mean and standard deviation.

Laboratory test values will be presented in individual patient listings, with flagging of values outside the normal ranges and marked normal ranges, by frequency tables for each parameter showing the numbers of patients with values outside normal ranges and marked normal ranges, and by shift tables for each parameter showing the numbers of patients with adverse changes from baseline.

Vital signs data and abnormalities at physical examination will be presented in individual patient listings.

8.7 Pharmacokinetics

Ceftobiprole plasma concentrations at each time point of measurement will be evaluated by descriptive statistics.

Pharmacokinetic data will be presented by individual listings and descriptive summary statistics.

8.8 DSMB analysis

An interim analysis of safety data will be performed by the DSMB after randomization of approximately 50 patients. The Blinded Investigator will remain blinded to the assigned treatment during this analysis (see Section 7.5).

9 STUDY ADMINISTRATION AND REGULATORY ASPECTS

9.1 Study records

The investigators (blinded and unblinded) must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

9.1.1 Investigator site file

The ISF must contain all essential documents as required by ICH E6 and applicable regulations, including the protocol and any subsequent amendments, CRFs, Query Forms, documented IEC/IRB approvals, documented regulatory approvals, sample informed consent forms, drug records, staff curriculum vitae, and other appropriate documents/correspondence.

9.1.2 Case report forms

For each patient enrolled in the study, including patients who do not complete the study and patients for whom a CRF is initiated during screening but are not randomized, a CRF must be completed and signed (manually or electronically) by the investigator (blinded and unblinded) or authorized centre staff. If a patient withdraws from the study, the reason must be noted on the CRF. If a patient is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

The investigator (blinded and unblinded) should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

If the CRF is to be the source document for certain data, this must be discussed and agreed with the Sponsor in advance, and clearly documented.

9.1.3 Patient source documents

Patient source documents used to record key efficacy/safety parameters, independent of the CRFs, may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, original laboratory reports, X-ray, pathology and special assessment reports, signed informed consent/assent forms, consultant letters, and patient screening and enrollment logs. Source documents are part of the study documents, and must be maintained and made available upon request for clinical monitoring visits, audits or inspections.

9.1.4 Document retention and archiving

The Principal Investigator must keep all study documents on file for at least 15 years after completion or discontinuation of the study. Subsequently, the Sponsor will inform the Principal Investigator when the study documents can be destroyed, subject to applicable regulations.

These files must be made available for audits and inspection, upon reasonable request, to the authorized representative of the Sponsor, or to regulatory authorities.

Should the Principal Investigator wish to assign the study records to another party, or move them to another location, the Sponsor must be notified in advance.

If the Principal Investigator cannot guarantee the archiving requirement at the investigational centre for any or all of the study documents, arrangements must be made between the Principal Investigator and the Sponsor for appropriate storage.

9.1.5 Sample retention

All samples taken will be stored for up to 5 years for future medical and/or scientific research projects related to ceftobiprole. Informed consent must be obtained for this purpose, authorizing the Sponsor to use their study information and samples for future research projects.

After a maximum of 5 years, all stored samples will be safely destroyed.

9.2 Clinical monitoring

Before study initiation, at a site initiation visit or at an Investigator's Meeting, the Sponsor will review the protocol, CRFs and other study documentation with the investigators (blinded and unblinded) and the centre staff.

The Monitor (blinded and unblinded) must visit the investigator (blinded and unblinded) and the study facilities on a regular basis throughout the study to verify adherence to Good Clinical Practice (GCP) and the protocol, and the completeness, consistency and accuracy of the data being entered into the CRFs. The unblinded monitor must also ensure that the study drug is being stored, dispensed, and accounted for according to specifications.

The Principal Investigator must ensure that the monitors have direct access to all required study data (source documents) during the regular monitoring visits. This includes all patient records needed to verify the entries in the CRFs.

The investigator (blinded and unblinded) must cooperate with the Monitors to ensure that any protocol deviations or other issues detected in the course of monitoring visits are resolved.

Monitoring reports (blinded and unblinded) must be written after each monitoring visit, per centre and per visit. These monitoring reports must be reviewed and approved by the respective supervisors (blinded and unblinded) of the Monitors.

Monitoring instructions are provided in the Clinical Monitoring Plan.

9.3 Audits and inspections

The study may be audited at any time, with appropriate notification, by qualified personnel from the Sponsor or its designees, to assess compliance with the protocol, GCP, and regulatory requirements. These audits may also be conducted for quality assurance purposes, to ensure that complete and accurate data are submitted, and that all AEs are being identified and reported in compliance with the protocol and applicable regulations. The study may also be inspected by regulatory authority inspectors, after appropriate notification.

In the event of an audit or an inspection, the investigators must ensure that direct access to all study documentation, including source documents, is granted to the auditors or inspectors.

9.4 Protocol amendments

Protocol amendments must be prepared by a representative of the Sponsor, and be reviewed and approved by the Project Physician and the Project Statistician.

All protocol amendments must be submitted to the appropriate IEC/IRB for information and approval in accordance with applicable laws and regulations, and to regulatory agencies if required.

Approval of a protocol amendment must be awaited before changes are implemented, with the exception of changes necessary to eliminate an immediate hazard to study participants, or changes involving only logistical or administrative aspects of the study (e.g., changes to monitors, changes to telephone numbers).

9.5 Premature termination of the study

The Sponsor reserves the right to terminate the study at any time. An investigator has the right to terminate his or her participation to the study at any time. Should either of these events occur, both parties will arrange the necessary procedures after review and consultation.

If the study is to be terminated early, the Sponsor and the investigators must ensure that adequate consideration is given to the protection of the interests of all patients enrolled in the study.

9.6 Publication policy

The Sponsor is committed to registering all therapeutic studies in a publicly accessible clinical trial registry (e.g., www.clinicaltrials.gov), and will ensure that results of these studies will be made available to the medical community consistent with applicable laws and regulations.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multicenter studies only in their entirety, and not as individual center data. Authorship is to be determined by mutual agreement.

The results of this study will be made available, e.g., submitted for publication and/or presentation at scientific meetings, in a timely manner. All manuscripts or abstracts must be submitted to the Sponsor prior to publication or presentation, allowing the Sponsor to protect proprietary information, and to provide comments based on information from other studies that may not yet be available to an investigator.

10 ETHICS AND GOOD CLINICAL PRACTICE

10.1 Good Clinical Practice

The study must be conducted in compliance with this protocol, ICH E6 and any relevant supplementary guidance on GCP, and applicable laws and regulations.

10.2 Informed consent and assent

It is the responsibility of the investigators, or a person designated by the investigators (if acceptable under local regulations), to obtain prior written informed consent from the subject's parent(s) or LAR for each individual participating in this study, after adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subject's parent(s) or LAR that they are completely free to refuse consent for the subject to enter the study, and to withdraw the subject from the study at any time for any reason. Appropriate forms for obtaining written informed consent will be provided by the Sponsor/designee, and reviewed by the IEC/IRB responsible for oversight of the study centre.

If appropriate, the subject's assent to participation in the study should be obtained by the investigator, at the same time as consent is obtained from the parent(s)/LAR. It is the responsibility of the investigator, after consultation with the parent(s)/LAR, to determine whether the subject is capable of forming an opinion and assessing the information provided about the study in order to agree to participate. This determination should not be based solely on the subject's age, but should also take into account other factors, including the subject's developmental stage, intellectual capacities, and life experience. Appropriate forms for obtaining the subject's assent to participation in the study will be provided by the Sponsor/designee, and reviewed by the IEC/IRB responsible for oversight of the study centre.

If the parent(s) or LAR are unable to read the informed consent form, an impartial witness should be present during the entire informed consent discussion. After the parent(s) or LAR have orally consented to the subject's participation in the study, the witness's signature on the form will attest that the information in the consent form was accurately explained to, and understood by, the parent(s) or LAR.

The CRFs for this study contain a section for documenting informed consent, which must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary. Parent(s) or LARs of all subjects who have not completed the last study follow-up visit must be informed of the new information, given a copy of the revised form, and asked to give their consent to the subject continuing in the study. Where the subject's assent has been given, this should also be obtained again after the new information has been explained to the subject in appropriate terms.

10.3 Patient confidentiality and data protection

The investigator (blinded and unblinded) must ensure that patient anonymity is maintained, and that patients' identities are protected from unauthorized parties. This includes any electronic data generated during the study. In the CRF, or other documents submitted to the Sponsor, patients must be identified only by an identification code, and not by name. The investigators must keep a confidential patient identification code list, as described in Section 8.3.21 of ICH E6.

The Sponsor is responsible for ensuring compliance with all applicable data protection laws.

10.4 Independent Ethics Committees / Institutional Review Boards

This protocol and any accompanying material provided to the patient, including patient information sheets or descriptions of the study used to obtain informed consent, as well as any advertising material and information about any compensation provided to the patient, must be submitted to an IEC/IRB operating in compliance with ICH E6 and any relevant supplementary guidance on GCP, and with applicable laws and regulations. Approval from the IEC/IRB must be obtained and documented before starting the study.

Amendments made to the protocol after receipt of IEC/IRB approval must also be submitted to the IEC/IRB in accordance with local procedures and applicable laws and regulations.

11 REFERENCES

(Abbanat 2014) Abbanat D, Shang W, Amsler K, et al. Evaluation of the *in vitro* activities of ceftobiprole and comparators in staphylococcal colony or microtitre plate biofilm assays. Int J Antimicrob Agents 2014; 43: 32–9.

(Awad 2014) Awad SS, Rodriguez AH, Chuang YC, et al. A Phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis. 2014;Jul 1;59(1):51–61.

(Blumer 1995) Blumer JL et al. 1995. Sequential, single-dose pharmacokinetic evaluation of meropenem in hospitalized infants and children. Antimicrob Agents Chemother 39:1721–5.

(Bogdanovich 2005) Bogdanovich T, Ednie LM, Shapiro S, et al. Antistaphylococcal activity of ceftobiprole, a new broad-spectrum cephalosporin. Antimicrob Agents Chemother 2005; 49: 4210–9.

(Bogdanovich 2006) Bogdanovich T, Clark C, Ednie L, et al. Activities of ceftobiprole, a novel broad-spectrum cephalosporin, against *Haemophilus influenzae* and *Moraxella catarrhalis*. Antimicrob Agents Chemother 2006; 50: 2050–7.

(Borbone 2010) Borbone S, Campanile F, Bongiorno D, et al. *In vitro* bactericidal activity of ceftobiprole against hospital- and community-associated methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 2010; 65: 591–4.

(Bradley 2011) Bradley JS, McCracken GH. Unique considerations in the evaluation of antibacterials in clinical trials for pediatric community-acquired pneumonia. Clinical Infectious Diseases 47:10.1086/596035, S241-S248.

(CSI-1004) Clinical Study Report (27 April 2007). An open-label, pharmacokinetic study of single and multiple intravenous infusions of ceftobiprole 500 mg administered to healthy adult subjects.

(CSI-1006) Clinical Study Report (1 October 2010). An open-label study to evaluate the single-dose pharmacokinetics and safety of ceftobiprole in pediatric subjects ≥3 months to <18 years of age undergoing treatment with systemic antibiotics.

(Davies 2007) Davies TA, Page MG, Shang W, et al. Binding of ceftobiprole and comparators to the penicillin-binding proteins of Escherichia coli, *Pseudomonas aeruginosa*, Staphylococcus aureus, and *Streptococcus pneumoniae*. Antimicrob Agents Chemother 2007; 51: 2621–4.

(Davies 2010) Davies TA, He W, Bush K, et al. Affinity of ceftobiprole for penicillin-binding protein 2b in *Streptococcus pneumoniae* strains with various susceptibilities to penicillin. Antimicrob Agents Chemother 2010; 54: 4510–2.

(Deshpande 2013) Deshpande A, Pasupuleti V, Thota P, et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. J Antimicrob Chemother 2013; 68: 1951–61.

(Entenza 2002) Entenza JM, Hohl P, Heinze-Krauss I, et al. BAL9141, a novel extended-spectrum cephalosporin active against methicillin-resistant *Staphylococcus aureus* in treatment of experimental endocarditis. Antimicrob Agents Chemother 2002; 46: 171–7.

(Farrell 2014) Farrell, D.J., Flamm, R.K., Sader, H.S., et al. Ceftobiprole activity against over 60,000 clinical bacterial pathogens isolated in Europe, Turkey, and Israel from 2005 to 2010. Antimicrob Agents Chemother 2014; 58: 3882-8.

(Hebeisen 2001) Hebeisen P, Heinze-Krauss I, Angehrn P, et al. *In vitro* and *in vivo* properties of Ro 63-9141, a novel broad-spectrum cephalosporin with activity against methicillin-resistant staphylococci. Antimicrob Agents Chemother 2001; 45: 825–36.

(Henry 2013) Henry X, Verlaine O, Amoroso A, et al. Activity of ceftaroline against Enterococcus faecium PBP5. Antimicrob Agents Chemother 2013; 57: 6358–60.

(Holliday 1957) Holliday, MA, Segar, WE. 1957. The maintenance need for water in parenteral fluid therapy. Pediatrics 19:823–32.

(Kosowska 2005) Kosowska K, Hoellman DB, Lin G, et al. Antipneumococcal activity of ceftobiprole, a novel broad-spectrum cephalosporin. Antimicrob Agents Chemother 2005; 49: 1932–42.

(Lemaire 2009) Lemaire S, Glupczynski Y, Duval V, et al. Activities of ceftobiprole and other cephalosporins against extracellular and intracellular (THP-1 macrophages and keratinocytes) forms of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2009; 53: 2289–97.

(Leonard 2008) Leonard SN, Cheung CM, and Rybak MJ. Activities of ceftobiprole, linezolid, vancomycin, and daptomycin against community-associated and hospital-associated methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2008; 52: 2974–6.

(Lovering 2012) Lovering AL, Gretes MC, Safadi SS, et al. Structural insights into the anti-methicillin-resistant Staphylococcus aureus (MRSA) activity of ceftobiprole. J Biol Chem 2012; 287: 32096–102.

(Lynch 2010) Lynch T, Bialy L, Kellner JD, et al. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. PLoS One 5:e11989.

(Michelow 2004) Michelow IC,, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004; 113:701–7.

(Muller 2014) Muller AE, Punt N, Mouton JW. Exposure to ceftobiprole is associated with microbiological eradication and clinical cure in patients with nosocomial pneumonia. *Antimicrob Agents Chemother* 2014;58:2512–4.

(Nicholson 2012) Nicholson SC, Welte T, File TM, Jr., et al. A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. *Int J Antimicrob Agents*. 2012;39:240–6

(Noel 2008a) Noel GJ, Bush K, Bagchi P, et al. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clin Infect Dis. 2008; 46: 647–55.

(Noel 2008b) Noel GJ, Strauss RS, Amsler K, et al. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. Antimicrob Agents Chemother. 2008; 52: 37–44.

(Parker 1995) Parker EM, Hutchison M, Blumer JL. The pharmacokinetics of meropenem in infants and children: a population analysis. Antimicrob Agents Chemother 1995; 36 (Suppl A):63–71.

(Queenan 2005) Queenan AM and Bush K. Johnson & Johnson Pharmaceutical Res. and Dev. L.L.C. Poster Abstract C1-55: Ceftobiprole: Effect on AmpC β-Lactamase Induction and Resistance Frequency in Gram-Negative Bacteria. ICAAC 2005 [data on file].

(Queenan 2007) Queenan AM, Shang W, Kania M, et al. Interactions of ceftobiprole with beta-lactamases from molecular classes A to D. Antimicrob Agents Chemother 2007; 51: 3089–95.

(Queenan 2010) Queenan AM, Shang W, Bush K, et al. Differential selection of single-step AmpC or efflux mutants of *Pseudomonas aeruginosa* by using cefepime, ceftazidime, or ceftobiprole. Antimicrob Agents Chemother 2010; 54: 4092–7.

(Rouse 2007) Rouse MS, Steckelberg JM, and Patel R. *In vitro* activity of ceftobiprole, daptomycin, linezolid, and vancomycin against methicillin-resistant staphylococci associated with endocarditis and bone and joint infection. Diagn Microbiol Infect Dis 2007; 58: 363–5.

(Shann 1999) Shann F, Steinhoff MC. 1999. Vaccines for children in rich and poor countries. Lancet 354 Suppl 2:S7–S11.

(Tam 2013) Tam PY. 2013. Approach to common bacterial infections: community-acquired pneumonia. Pediatr Clin North Amer 60:437–53.

(TOX8611) Ceftobiprole medocaril (BAL5788): A subcutaneous toxicity study in neonatal and juvenile albino rats. Charles River Laboratories Preclinical Services Montreal Inc. Study No. 901275. Document ID No. EDMS-PSDB-9243880; J&JPRD (12 Nov 2008).

(Woods 2013) Woods CR and Bryant KA. 2013. Viral infections in children with community-acquired pneumonia. Curr Infect Dis Rep 15:177–83.

Appendix 1 Rationale for ceftobiprole dosage selection (paediatric population aged 3 months to < 18 years)

Overview

The ceftobiprole doses selected for this study are:

Age group	Dosing regimen up to a maximum of 500 mg
3 months to < 2 years	20 mg/kg as a 4-h infusion q8h
2 years to < 6 years	20 mg/kg as a 2-h infusion q8h
6 years to < 12 years	15 mg/kg as a 2-h infusion q8h
12 years to < 18 years	10 mg/kg as a 2-h infusion q8h

The selection of this dosing regimen was based on the following five considerations:

1. The level of drug exposure that have been demonstrated to be effective in treating HAP and CAP (in adults)
2. The pharmacokinetic and safety results of a previous single-dose study in paediatric subjects aged 3 months to < 18 years (study CSI-1006)
3. Adverse event profile of ceftobiprole in adults
4. The results of a toxicity study in juvenile animals
5. Pharmacokinetic modeling results

Target drug exposure and efficacy considerations

Ceftobiprole is a cephalosporin and belongs to the beta-lactam class of antibiotics. For beta-lactam antibiotics, it is well established that the time (T) that plasma concentrations of drug are above the minimum inhibitory concentration (MIC) for a given pathogen (T>MIC) correlates well with therapeutic efficacy[*]. For ceftobiprole an unbound T>MIC corresponding to ≥50% of the drug dosing interval (e.g., 4 hours for a drug given every 8 hours) for broad spectrum coverage was demonstrated in preclinical studies[†] and in the Phase 3 studies in nosocomial pneumonia (BAP248/307)[‡] and in community-acquired pneumonia (CAP-3001)[§].

Accordingly, considering that ceftobiprole will be used as a broad-spectrum antibiotic, a dosing regimen leading to unbound (*f*) plasma drug levels above a non-species related breakpoint MIC of 4 µg/mL for at least 50% of the dosing interval is the target. The efficacy of ceftobiprole in paediatric subjects is expected to be similar to that in adults if the %*f*T>MIC with regard to ceftobiprole plasma levels is comparable.

---

[*] Craig. Does the dose matter? *Clin Infect Dis* 2001;33:233–237

[†] Craig. *In vivo* pharmacodynamics of ceftobiprole against multiple bacterial pathogens in murine thigh and lung infection models. *Antimicrob Agents Chemother* 2008; 52:3492–3496

[‡] Muller. %*ft.*>MIC predicts probability of clinical outcome in the treatment of nosocomial pneumonia by ceftobiprole. ECCMID 2013 Poster P904

[§] Muller. %*ft.*>MIC predicts the microbiological eradication at end of treatment with ceftriaxone or ceftobiprole in patients with community acquired pneumonia. ICAAC 2013 Poster A-472

Previous pharmacokinetic and safety results

Experience in adults

The disposition of ceftobiprole is linear in the dose range investigated (from 250 mg to 1000 mg). The half-life is approximately 3 hours with limited accumulation after repeated every 8-hour (q8h) administration. The pharmacokinetics are highly reproducible, with a low inter-and intra-subject variability. Ceftobiprole is distributed in the extracellular compartment (18 L), and is weakly bound to plasma proteins (16%). Its elimination is predominantly renal by passive glomerular filtration (> 80% of the dose recovered as unchanged drug in urine); creatinine clearance is therefore the main driver of exposure to ceftobiprole.

Ceftobiprole was well tolerated in adult healthy subjects and patients in clinical studies, with the main reported treatment-emergent adverse events (AEs) being dysgeusia, nausea and vomiting. In pooled safety data from 2 Phase 3 studies in subjects with complicated skin and soft tissue infections (dosing regimens of 500 mg q12h 1-h infusion and 500 mg q8h 2-h infusion), the incidence of these AEs was not related to the dose but was rather related to the infusion duration, suggesting a Cmax related effect. The dose regimen that was primarily investigated in Phase 3 studies in adult subjects with complicated skin and soft tissue infections, community-acquired pneumonia and nosocomial pneumonia was 500 mg q8h as a 2-h infusion. Multiple doses up to 1000 mg q8 as a 1.5-h infusion were also investigated in adult healthy subjects, and were well tolerated.

Experience in juvenile animals

A study was conducted in neonatal and juvenile male and female rats commencing on post-partum Day 1 up to 50 days, followed by a 28-day recovery period. Exposure to ceftobiprole was determined in each dose group investigated throughout the study. The NOAEL in this study was determined to be 100 mg/kg/day [TOX8611].

The corresponding exposures are summarized in Table A1.

Table A1 Exposure to ceftobiprole at the NOAEL in juvenile rats

100 mg/kg/day s.c.		**Female rats**		**Male rats**	
Study day post-partum	**Approximate human equivalent age**	**C_{max} (µg/mL)**	**AUC_{0-8h} (µg.h/mL)**	**C_{max} (µg/mL)**	**AUC_{0-8h} (µg.h/mL)**
Day 1	neonate	65.9	261	55.7	265
Day 18	~ 6 years	101	133	92.6	148
Day 49	~ 14 years	84.0	119	76.1	139

Experience in the paediatric population

Study CSI-1006 evaluated the pharmacokinetics of ceftobiprole when administered as a single dose in paediatric subjects 3 months to < 18 years of age who required therapeutic or prophylactic therapy with systemic antibiotics. Subjects were enrolled and dosed according to 4 age groups: 3 months to < 2 years (15 mg/kg dose), 2 years to < 6 years (15 mg/kg), 6 years to < 12 years (10 mg/kg), and 12 years to < 18 years (7 mg/kg).

In the pharmacokinetic evaluable subset, ceftobiprole volume of distribution and systemic clearance increased with age to reach almost healthy-adult historical values in the 12 to < 18 years age group [CSI-1006].

At the doses administered in this study to subjects < 12 years of age (15 mg/kg for subjects < 6 years and 10 mg/kg for subjects 6 years to < 12 years), the single-dose pharmacokinetics of ceftobiprole were generally within the range of what has previously been observed in healthy adult subjects after a single ceftobiprole 500 mg dose (q8h 2-h infusion), i.e., 62.3%–90.1% [CSI-1004].

However, at the doses investigated, in each age group there were children underexposed in terms of the PD target [CSI-1006]. Observed pharmacokinetic and pharmacodynamic parameters corrected by the free fraction in the different age groups are presented in Table A2.

Table A2 Observed pharmacokinetic and pharmacodynamics parameters corrected by the free fraction in the different age groups (study CSI-1006)

Ceftobiprole dose administered as 2-h infusion (single dose)				
Age group	**3 months to < 2 years**	**2 years to < 6 years**	**6 years to < 12 years**	**12 years to < 18 years**
Investigated doses	**15 mg/kg**	**15 mg/kg**	**10 mg/kg**	**7 mg/kg**
$T_{1/2}$ (h)	2.1 (1.1-4.1)	2.0 (1.6-2.8)	2.1 (1.5-3.2)	2.4 (1.9-1.2)
fC_{max} (µg/mL)	18.9 (8.22-41.2)	22.9 (12.8-35.9)	21.2 (16.7-26.8)	14.2 (7.36-19.4)
f$AUC_{0\text{-}8h}$ (µg.h/mL)	60.4 (25.2-124)	65.7 (34.0-101)	61.0 (33.9-77.0)	45.4 (28.1-61.1)
*f*T>MIC = 4 µg/mL (h)	5.3 (2.8-7.5)	5.3 (3.4-7.4)	5.0 (3.5-6.7)	4.5 (3.0-6.0)
Number of subjects below the target of 50% of dosing interval	2 out of 16	3 out of 15	1 out of 15	4 out of 15

The safety profile observed in study CSI-1006 after single-dose administration of ceftobiprole (7 mg/kg to 15 mg/kg) in paediatric subjects receiving other systemic antibiotic therapy was generally similar that observed in adults. No new or unexpected safety signals associated with study drug were detected. Thirty-one subjects (48%) reported at least 1 treatment-emergent AE. The majority of treatment-emergent AEs were mild in severity and considered not related to study drug. The most common AEs were vomiting (reported in 6 subjects [9%]) and pruritus (reported in 3 subjects [5%]). No deaths or drug-related SAEs were reported during the study. No subjects discontinued due to a treatment-emergent AE [CSI-1006].

Pharmacokinetic modeling

The modeling strategy was to optimize the dosing regimen (dose, dosing interval and infusion duration) for paediatric subjects 3 months – < 18 years in order to maximize *f*T>MIC=4 µg/mL and maintain exposure in the range well tolerated range by adults, and below the exposure at the NOAEL in the juvenile rat study [TOX8611] for the corresponding age groups.

Several variables were explored: incremental higher doses (up to 25 mg/kg), infusion times (2 or 4 hours), dosing regimen (q6h or q8h), and combinations of these variables. Total and unbound parameters were generated using a free fraction of 0.84 as reported in adults. The optimized regimens for paediatric subjects of various age groups are summarized in Table A3.

Table A3 Predicted exposure to ceftobiprole in the various age groups 3 months to < 18 years

Age group	3 months to < 2 years	2 years to < 6 years	6 years to < 12 years	12 years to < 18 years
Number of subjects	16	15	15	15
Recommended regimen*	20 mg/kg over 4-h q8h	20 mg/kg over 2-h q8h	15 mg/kg over 2-h q8h	10 mg/kg over 2-h q8h
ft>MIC=4 µg/Ml below 50% of dosing interval	0	0	0	1
Above highest adult C_{max}	0	0	0	0
Above highest adult AUC	1	0	0	0
Above exposure (C_{max} and AUC) at NOAEL	0	0	0	0

* Up to a maximum of 500 mg.

Appendix 2 Criteria for evaluating relationship between adverse events and study treatment

NOT RELATED

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the study drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the study drug was interrupted or stopped the event did not improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the study drug, yet study drug-relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias.). If the study drug was re-administered it did not reappear.
2. It does not follow a known pattern of the response to the suspected study drug or drugs of the same substance class.
3. It is judged to be clearly and incontrovertibly due only to extraneous causes such as the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

UNLIKELY

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the study drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the study drug was interrupted or stopped the event did not improve or disappear. If the study drug was re-administered it did not reappear.
2. It does not follow a known pattern of the response to the suspected study drug or drugs of the same substance class.
3. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

POSSIBLE

This category is applicable to an AE that does not meet the criteria for 'not related' or 'unlikely', nor the criteria for 'probable'. An AE would be considered possible if, or when e.g.:

1. It follows a reasonable temporal sequence from administration of the study drug (see also additional explanations above) or it follows a known pattern of the response to the suspected study drug or drugs of the same substance class.
2. It may or may not have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

Note: If an event neither follows a plausible temporal relationship nor a known pattern of response but there is no alternative explanation for the event, this will usually be judged a possibly related event.

PROBABLE

This category is applicable to an AE that is considered, with a high degree of certainty, to be related to the study drug. An AE may be considered probable, if it meets the following three criteria:

1. It follows a reasonable temporal sequence from administration of the study drug, i.e., the time between the administration of study drug and occurrence of the event is plausible. If the study drug was interrupted or stopped the event did improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the study drug, yet drug-relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias.) If the study drug was re-administered it did reappear.
2. It follows a known pattern of the response to the suspected study drug or drugs of the same substance class.
3. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

Regardless of the criteria mentioned above, reappearance of an event upon re-challenge must be regarded as strong evidence of probable relationship to study drug.

A causal relationship is suspected for all AEs/SAEs reported with a relationship of 'possible' or 'probable' and those with missing or unknown relationships.

Appendix 3 Investigator's protocol signature page

BASILEA

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol	BPR-PIP-002 Version 3.0	Basilea Product:	Ceftobiprole
Protocol 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**		

Basilea Pharmaceutica International Ltd

Approval Date: 29 November 2018 By (Project Physician): [redacted] MPH

Name of Principal Investigator:

Study Centre:

I agree to the conditions relating to this study as set out in the above named Protocol and Study Procedures. I fully understand that any changes instituted by the investigator(s) without previous discussion with the Sponsor's Project Clinician, Clinical Pharmacologist and Biostatistician (only if required) would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well-being of the subjects).

I agree to follow International Conference on Harmonisation (ICH) guidelines for good clinical practice (GCP), including the EU Clinical Trial Directive 2001/20/EC and specifically, obtain approval from the Ethics Committee prior to study start, allow direct access to source documents and agree to inspection by auditors from Basilea and regulatory authorities, as required by ICH GCP. I will ensure that the investigational product(s) supplied by the Sponsor will be used only as described in the above named protocol; if *any* other use is desired, *written permission* must be obtained from the Sponsor.

I acknowledge that I have read the protocol for this study, and I agree to carry out all of its terms in accordance with applicable laws and regulations.

To be signed by Principal Investigator and Sub-Investigators (at minimum):

Please print names and dates next to the corresponding signatures

Signature	**Name**	**Date**
	Principal Investigator	
	Sub/Co-Investigator	