CLINICAL STUDY PROTOCOL

BPR-PIP-001

Ceftobiprole medocaril

Version 5.0 / 21 March 2019

An open-label study to evaluate the single-dose pharmacokinetics and safety of ceftobiprole in neonate and infant subjects aged up to 3 months undergoing treatment with systemic antibiotics
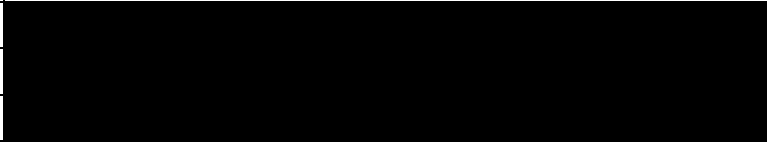
Protocol number/Version:	BPR-PIP-001 / Version 5.0
Compound:	Ceftobiprole medocaril
Phase of development:	Phase 1
EudraCT number:	2013-004614-18
Project Physician:	
Project Pharmacologist	
Project Statistician:	
Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel/Switzerland Tel + 41 61 606 1111

Note: This is an electronically controlled document.

SPONSOR SIGNATURES

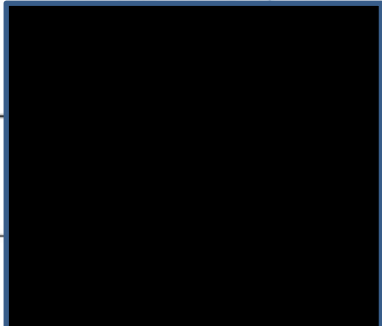| Protocol Number/Version:	BPR-PIP-001 / Version 5.0
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Name/Title	Date	Signature
Project Physician	21 – Mar-2019	
Project Pharmacologist	21-MAR-2019	

PROTOCOL SYNOPSIS

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

Sponsor: Basilea Pharmaceutica International Ltd

Project Phase: 1

Indication: Clinical pharmacology

Objectives

Primary: to characterize the pharmacokinetics of single doses of ceftobiprole in neonates and infants aged ≤ 3 months.

Secondary: to evaluate the safety and tolerability of ceftobiprole in neonates and infants aged ≤ 3 months.

Study design: Open-label, single-fixed dose, multicenter study

Planned total sample size

45 neonate or infant subjects, stratified for gestational age and post-natal age

Number of centers and recruitment

Up to 8 centers in Europe, and 10 centers in the USA, with additional centers and locations possible

Subject inclusion criteria

1. Neonates and infants ≤ 3 months, with gestational age ≥ 28 weeks
2. Documented or presumed (or at risk of) bacterial infections, and currently receiving antibiotic treatment[*]
3. Expected to survive beyond the first 7 days after enrolment
4. Sufficient vascular access to receive study drug, and to allow blood sampling at a site separate from the study drug infusion site
5. Parent's / legally acceptable representative's informed consent to participate in the study

[*] Subjects must be scheduled to receive at least one infusion of systemic antibiotics before, and at least one infusion after, their ceftobiprole dose.

Subject exclusion criteria

1. Major birth defect or malformation syndrome[+]
2. Proven presence of an immunodeficiency
3. HIV or other congenital viral or fungal infection
4. Significant laboratory abnormalities including:
   - Haematocrit < 20%
   - Absolute neutrophil count (ANC) < 0.5×10^9/L
   - Platelet count < 50×10^9/L
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) > 3 × the age-specific upper limit of normal (ULN)

5. Impaired renal function or known significant renal disease, as evidenced by an estimated glomerular filtration rate (using the Schwartz formula or other applicable formula) less than 2/3 of normal for the applicable age group[‡]

6. Any condition which would make the subject or caregiver, in the opinion of the investigator, unsuitable for the study

[+] Subject eligibility will be decided based on an individualized assessment. Subjects with major birth defects or malformation syndromes should be excluded in view of the following

- A low likelihood that the subject will complete the study

- Increased risk of side effects with ceftobiprole (e.g. seizures in patients with CNS disorders)

- An expected impact on pharmacokinetics (e.g., haemodynamically relevant shunts)

[‡] See Appendix 4 for supporting data and the table of GFR thresholds.

Study drugs and formulations:
Ceftobiprole medocaril powder for concentrate for solution for infusion (BAL5788)

Concurrent control: None

Study drug dosage
7.5 mg/kg body weight ceftobiprole (single-dose), administered as ceftobiprole medocaril

Route of administration
Intravenous

Blinding
Open-label

Duration of subject participation
Total duration 8 ± 3 days, comprising 24-hour screening, administration of a single dose of ceftobiprole, and 6 ± 3-day follow-up

Main parameters

Efficacy
Not applicable

Safety and tolerability
Adverse events, laboratory tests (hematology, blood chemistry, urinalysis), vital signs, physical examination

Pharmacokinetics
Non-compartmental analysis : C_{max}, $t_{1/2}$ AUC_{0-t}, $AUC_{0-\infty}$, CL_S, V_{SS}, $T > MIC$.

The relationship between exposure (C_{max} and AUC), derived pharmacokinetic (PK) parameters (CL_S, V_{SS}, $t_{1/2}$) gestational age, post-natal age, body weight, body mass index, body surface area, and calculated creatinine clearance will also be assessed.

Statistical analysis
No hypothesis testing will be performed. PK data will be listed and analysed using descriptive statistics, including mean, median, SD, %CV, and range. Safety data will be listed and presented in frequency tables, summary tables, and shift tables.

Analysis populations

Pharmacokinetics analysis population: all subjects who receive study drug and have adequate samples for determination of time-plasma concentration profiles of ceftobiprole.

Safety analysis population: all subjects who receive any quantity of study drug.

PROCEDURES

A total of 45 male and female neonates and infants aged up to 3 months (inclusive) will be assigned to study treatment. Subjects must be undergoing treatment with systemic antibiotics for documented or presumed bacterial infections, or because they are at risk of infection. The study population will comprise 3 cohorts, each of 15 subjects, based on gestational age (28 to 32 weeks [completed]; 33 to 36 weeks [completed]; ≥ 37 weeks). In the two cohorts with subjects of gestational age ≤ 36 weeks, subjects will be further stratified by post-natal age (< 28 days; ≥ 28 days) so that at least 5/15 subjects are assigned to study treatment in each post-natal age group. Cohorts will be sequentially dosed, with the first cohort comprising subjects of the highest gestational age.

Parents or legally acceptable representatives will provide signed informed consent. Subjects in each cohort will be screened for eligibility within 24 hours before dosing. Enrolled subjects will be dosed in specialised neonatal care institutions/departments.

Subjects will receive a single dose of ceftobiprole at 7.5 mg/kg body weight, given as a 4-hour constant-rate infusion of ceftobiprole medocaril. Blood samples (200–300 µL) for PK analysis will be obtained at baseline (pre-dose), and at 2, 4, 6, 8 and 12 hours after the start of dosing. Full portions of urine will be collected in subjects in whom a urinary catheter has been placed for their standard clinical care; urinary catheters will not be placed for the purpose of the study. In subjects without a urinary catheter, one or more portions of urine may be obtained before, during, and after dosing.

An aliquot of the infusion solution will be collected and frozen at below −65 °C immediately after sampling for analysis, to ensure that the correct dose was given. Subjects will be evaluated for safety on Day 7 ± 3 after dosing.

Efficacy will not be evaluated. Safety assessments will include vital signs, physical examination, safety laboratory tests, and monitoring for adverse events.

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ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
BLQ	Below the limit of quantitation
BUN	Blood urea nitrogen
CHO	Chinese hamster ovary
CL_{CR}	Creatinine clearance
C_{max}	Maximum observed plasma concentration
CLs	Systemic clearance
CPK	Creatinine phosphokinase
CV	Coefficient of variation (%CV)
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalogram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee / Institutional Review Board
i.v.	Intravenous
LC	Liquid chromatograph
LDH	Lactate dehydrogenase
LOQ	Limit of quantitation

MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MIC	Minimum inhibitory concentration
MS	Mass spectrometry
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PMA	Post-menstrual age
PK	Pharmacokinetic(s)
QC	Quality control
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
$T > MIC$	Time that concentration is above the MIC
$t_{1/2}$	Half life
t.i.d.	Three times daily
ULN	Upper limit of normal
Vss	Volume of distribution at steady-state
WBC	White blood cell

1 INTRODUCTION AND BACKGROUND

1.1 Disease characteristics and treatment

Bacterial infection is a leading cause of morbidity and mortality in children. Bacterial infections in children may be caused by a wide range of Gram-positive or Gram-negative pathogens, including group B streptococci, coagulase-negative staphylococci, Methicillin-resistant *Staphylococcus aureus* and Gram-negative organisms [1–4]. Initial therapy in infants with severe infections is generally empiric because pathogen identification often requires impractical invasive sampling [3]. Accordingly, it is important to use antimicrobials that provide broad-spectrum antibacterial activity [5].

1.2 Ceftobiprole medocaril

1.2.1 Nonclinical studies

1.2.1.1 Pharmacology/microbiology/pharmacokinetics/pharmacodynamics.

Ceftobiprole medocaril (BAL5788) is the water-soluble prodrug of ceftobiprole, a cephalosporin with bactericidal activity against a broad spectrum of Gram-positive bacteria, including methicillin-resistant *Staphylococcus* species, vancomycin-resistant *S. aureus*, and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Ceftobiprole also demonstrates activity against Gram-negative bacteria, including *Pseudomonas aeruginosa*. Ceftobiprole is formulated for intravenous administration. Ceftobiprole is resistant to hydrolysis by the *S. aureus* PC1 Class A β-lactamase, and is relatively resistant to hydrolysis by many β-lactamases of Class C and Class A Gram-negative bacteria. Ceftobiprole is hydrolyzed by extended spectrum β-lactamases and metallo β-lactamases.

The pharmacokinetic/ pharmacodynamic (PK/PD) parameter best correlating with efficacy was the time that the drug concentration exceeded the MIC (T > MIC), as for other β-lactam antibiotics.

Protein binding of ceftobiprole in plasma in all animal 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 intravenous administration of ceftobiprole medocaril.

Further details on the pharmacology, microbiology, PK and PD of ceftobiprole medocaril are provided in the Investigator's Brochure (IB).

1.2.1.2 Toxicology

In animals, the primary targets of toxicity after intravenous administration 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 resulting renal tissue damage. This effect is not thought to apply to humans because glomerular filtration of ceftobiprole is much slower and urinary concentrations of ceftobiprole do not approach the limit of solubility.

- Local tolerance**:**
  - In small animals (4 or 13 week studies in rats or marmosets) concentration-dependent slight to moderate local endothelial irritation was observed when ceftobiprole medocaril (prodrug) was administered over 4–8 hours into the Vena cava at concentrations up to 62 mg/mL.
  - In a local tolerability study in rabbits, repeated intravenous administration of ceftobiprole into the auricular vein (8 consecutive days with a 3-minute endothelial contact period per day) caused no irritation at concentrations of 2 and 10 mg/mL (corresponding to ceftobiprole medocaril sodium nominal 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.
  - In a previous clinical study including 64 children age 3 months to 17 years when ceftobiprole was administered intravenously at a concentration of 2 mg/mL as single dose over 2-hours (at dose levels of 7, 10, or 15 mg/kg) one moderate catheter-site related reaction was observed in a child in the age group ≥ 2 to < 6 years (ceftobiprole 15 mg/kg) and one mild phlebitis in a child in the age group ≥ 3 months to < 2 years (ceftobiprole 15 mg/kg). Overall, the available non-clinical and clinical data suggest that the expected risk of local irritation in the paediatric population with ceftobiprole is acceptable.

- Ceftobiprole medocaril 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 sensitization, irritation, or phototoxicity were seen. The antigenic potential of ceftobiprole medocaril is low. No mutagenic potential was seen in the Ames test or in the Chinese hamster ovarian (CHO HGPRT) assay, and *in vivo* genotoxicity assays (micronucleus and unscheduled DNA synthesis assays).

- The convulsive potential after intracerebroventricular administration to mice was comparable to that of imipenem. No cardiac or pulmonary toxicity was observed.

- Neonatal and juvenile rats (one 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 were 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 no-observed-adverse-effect level (NOAEL) in juvenile animals was 100 mg/kg/day (corresponding to 75 mg/kg/day of ceftobiprole).

- Safety margins based on plasma exposures noted at the NOAEL in animals are approximately 1- to 5-fold and 1- to 3-fold for C_{max} and 2- to 3-fold and 1- to 2-fold for AUC for administration of 500 and 1,000 mg ceftobiprole (BAL9141) infused to humans over 2 hours as ceftobiprole medocaril (BAL5788). The safety margin based on plasma concentrations of ceftobiprole seen at the no-observed-effect level (NOEL) for renal toxicity is 2- to 7-fold and 1- to 5-fold relative to clinical doses of 500 and 1,000 mg, whereas 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 are applicable to single-dose or multiple-dose administration, since drug accumulation is negligible with multiple dosing in humans.

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

1.2.2 Clinical studies

1.2.2.1 Clinical pharmacology

The PK of ceftobiprole in adult subjects are predictable, linear and time-independent across the dose range of 125 to 1,000 mg, and variability is low ($<30\%$). 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. Therefore dose regimen adjustments are recommended in adult subjects with moderate and severe renal impairment, in end-stage renal disease subjects and in subjects with $CL_{CR} > 150$ mL/min.

In paediatric subjects given single doses of ceftobiprole at 15 mg/kg (age 3 months to <6 years), or 10 mg/kg dose (age 6 years to <12 years), the single-dose PK of ceftobiprole were generally within the range of what has previously been observed in healthy adult subjects after a single ceftobiprole 500 mg dose. However, in subjects given 7 mg/kg (age 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* as being age-independent from neonates to adults.

Further details on the clinical pharmacology of ceftobiprole medocaril are provided in the IB.

1.2.2.2 Efficacy and safety

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

In a previous clinical study in 64 paediatric subjects age 3 months to 17 years (study CSI1006), ceftobiprole was administered intravenously 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 subjects). 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 subjects discontinued due to a treatment-emergent AE.

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

Further details on the clinical efficacy and safety of ceftobiprole are provided in the IB.

1.2.3 Rationale for dose selection and treatment period

Neonate and infant subjects will receive a single infusion of 7.5 mg/kg ceftobiprole, administered as ceftobiprole medocaril, as a 4-hour continuous-rate infusion. The planned dose of ceftobiprole is justified by the results of study CSI1006, in which paediatric subjects aged 3 months to < 2 years received 15 mg/kg ceftobiprole [6], by PK modeling results and by the experience in the paediatric population with other beta-lactams.

A detailed dosing rationale is provided in Appendix 1. A single-dose study is sufficient to determine the PK of ceftobiprole in subjects while minimizing risk. The results of a single-dose study may be predictive of multiple-dose PK if the clearance of ceftobiprole is high and the potential for drug accumulation is minimal.

2 OBJECTIVES OF THE STUDY

2.1 Primary objective

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

2.2 Secondary objective

The secondary objective is to evaluate the safety and tolerability of ceftobiprole in neonates and infants aged ≤ 3 months.

3 STUDY DESIGN

3.1 Overview of study design and dosing regimen

This is an open-label, single-fixed-dose, multicenter study to be carried out in three sequential cohorts, each of 15 neonates or infants aged ≤ 3 months (45 subjects total). The study will be conducted mainly in European centers and centers in the USA, but additional centers or other countries may be considered.

The study comprises (i) a pre-dosing screening phase of up to 24 hours, (ii) a 1-day dosing phase with single-dose intravenous administration of ceftobiprole at 7.5 mg/kg, and (iii) a post-dose follow up safety assessment on Day 7 ± 3 after ceftobiprole administration.

Table 1 provides an overview of the study design.

Table 1 Summary of treatment and follow-up schedule

Screening Day –1	Single intravenous infusion of ceftobiprole over 4 hours Day 1	Follow-up Day 7±3
	Ceftobiprole medocaril equivalent to 7.5 mg/kg ceftobiprole	

This study will assign to treatment with ceftobiprole 45 male or female neonates and infants aged up to 3 months (inclusive) who are already undergoing treatment with systemic antibiotics for documented or presumed bacterial infections, or because they are at risk of infection.

The study population will comprise 3 cohorts, each of 15 subjects, based on gestational age: 28 to 32 weeks [completed]; 33 to 36 weeks [completed]; ≥ 37 weeks.

In the two cohorts with subjects of gestational age ≤ 36 weeks, subjects will be further stratified by post-natal age (< 28 days; ≥ 28 days) so that at least 5/15 subjects are assigned to study treatment in each post-natal age group.

Cohorts will be sequentially dosed, with Cohort 1 comprising subjects of the highest gestational age (see Sections 3.3 and 6.1). In Cohorts 2 and 3, dosing will not start until at least 5 subjects in the previous cohort have completed dosing as planned and the follow-up safety evaluation (Day 7±3).

Parents or legally acceptable representatives will provide signed informed consent. Informed consent must be obtained within 3 days prior to dosing on Day 1. Subjects in each cohort will be screened for eligibility within 24 hours before dosing. Enrolled subjects will be dosed in specialised neonatal care institutions/departments with support to allow parents/legally acceptable representatives or caregivers to stay close to their children, and staff trained in minimising stress and discomfort associated with blood sampling and urine sampling (if possible) for PK assessments.

Dosing with ceftobiprole should be scheduled so that the 4-hour infusion and subsequent assessments do not conflict with the ongoing treatment with systemic antibiotic(s) or routine infant care. Blood samples (200–300 µL) for PK analysis will be obtained at baseline (pre-dose), and at 2, 4, 6, 8 and 12 hours after the start of dosing. Urine samples for sparse PK analysis will be collected (if possible) before, during, and after dosing. An aliquot of the infusion solution will be collected for analysis, to ensure that the correct dose was given. Subjects will be evaluated for safety on Day 7 ± 3 after dosing.

Efficacy will not be evaluated. Safety assessments will include vital signs, physical examination, safety laboratory tests, and monitoring for AEs.

3.2   Discussion of study design

The study design is conventional, and adequate for the determination of standard single-dose PK outcomes in neonates and infants. Blood sampling is minimal, but adequate to describe profiles of plasma drug concentration over time for each subject. Sparse urine PK sampling is intended to confirm successful administration of ceftobiprole, and to confirm renal elimination as unchanged drug plus ring-open metabolite, as observed in adults and children aged > 3 months.

Safety measures include the selection of clinics specialized in neonatal care, the use of staff trained in minimizing infant stress and discomfort, and the sequential dosing and safety evaluation of full-term infants or neonates, followed by pre-term infants or neonates. Safety evaluations are practical, routine in neonate and infant care, and do not impose needless discomfort. Since eligible subjects will already be receiving an intravenous antibiotic, the administration of ceftobiprole does not impose substantial additional discomfort or risk.

3.3   Number of subjects/ assignment to treatment groups

A total of 45 neonates and infants will be assigned to study treatment, comprising 3 cohorts to be dosed sequentially in the following order:

Cohort 1: 15 subjects with gestational age ≥ 37 weeks.

Cohort 2: 15 subjects with gestational age 33 to [completed] 36 weeks.

Cohort 3: 15 subjects with gestational age 28 to [completed] 32 weeks.

Cohorts 2 and 3 will be further stratified by post-natal age (≥ 28 days, or < 28 days) so that at least 5 subjects are assigned to study treatment in each group.

The safety data and PK data of the first 3 subjects of Cohort 1 will be reviewed by the investigators and the sponsor's clinical and drug safety representatives prior to dosing of subsequent subjects.

In Cohorts 2 and 3, dosing may not start until at least 5 subjects in the prior cohort have completed dosing as planned, the follow-up safety assessments have been completed, and safety and PK data have been reviewed by the investigators and the sponsor.

The investigators and the sponsor will have regular consultation meetings or tele-conferences to assess the safety and PK data during the course of the study. These meetings to review safety and PK data will be held whenever 5 new subjects (dosed in any cohort) have completed dosing and safety follow-up, and their PK data have been analysed. Consultation meetings may be conducted more frequently if required. Pharmacokinetic analyses will be provided in a timely fashion during the study.

The discussion and consensus decision-making of the consultation meetings between the investigators and the sponsor's clinical and drug safety representatives will be governed by a charter and documented in minutes.

3.4 Centers

This study will be carried out in approximately 8 study centers in Europe, and in 10 centers in the USA. In the event of slow recruitment, additional centers may be considered.

4 STUDY POPULATION

4.1 Target population

The target population comprises male and female neonates and infants aged up to 3 months (inclusive) who are undergoing treatment with systemic antibiotics for documented or presumed bacterial infections, or because they are at risk of infection.

4.2 Inclusion criteria

Subjects must meet all of the following criteria to be assigned to study treatment:

1. Neonates and infants ≤ 3 months, with gestational age ≥ 28 weeks
2. Documented or presumed (or at risk of) bacterial infections, and currently receiving antibiotic treatment[*]
3. Expected to survive beyond the first 7 days after enrolment
4. Sufficient vascular access to receive study drug, and to allow blood sampling at a site separate from the study drug infusion site
5. Parent's / legally acceptable representative's informed consent to participate in the study

[*] Subjects must be scheduled to receive at least one infusion of systemic antibiotics before, and at least one infusion after, their ceftobiprole dose.

4.3 Exclusion criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Major birth defect or malformation syndrome[+]

2. Proven presence of an immunodeficiency

3. HIV or other congenital viral or fungal infection

4. Significant laboratory abnormalities including:
   - Haematocrit $< 20\%$
   - Absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L
   - Platelet count $< 50 \times 10^9$/L
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $> 3 \times$ the age specific upper limit of normal (ULN)

5. Impaired renal function or known significant renal disease, as evidenced by an estimated glomerular filtration rate (using the Schwartz formula or other applicable formula) calculated to be less than 2/3 of normal for the applicable age group[‡]

6. Any condition which would make the subject or caregiver, in the opinion of the investigator, unsuitable for the study

[+] Subject eligibility will be decided based on an individualized assessment. Subjects with major birth defects or malformation syndromes should be excluded in view of the following
   - A low likelihood that the subject will complete the study
   - Increased risk of side effects with ceftobiprole (e.g. seizures in patients with CNS disorders)
   - An expected impact on pharmacokinetics (e.g., haemodynamically relevant shunts)
[‡] See Appendix 4 for supporting data and the table of GFR thresholds.

4.4 Criteria for premature withdrawal and replacement of subjects

While premature withdrawal is generally not applicable to a single-dose study, the 4-h infusion may be stopped at the investigator's discretion in the event of adverse reactions (including but not limited to allergic-type reactions, infusion site reactions, or clinically relevant changes in vital signs), or in the event of apparent infant distress, or at the request of the parent or the legally acceptable representative.

If the infusion is stopped, the exact time of the termination will be entered into the electronic case report form (eCRF).

Subjects who do not receive the complete infusion may be replaced by enrolment of a new subject meeting the same cohort definitions of gestational and post-natal age (see Section 3.3).

4.5 Concomitant and previous medication and treatment

Each subject will receive treatment with systemic antibiotics (based on clinical grounds) as prescribed by the investigator. Subjects may also receive other medication and treatment, without restriction, at the investigator's discretion.

All medication given to the subject during the course of the study will be entered into the eCRF; information to be recorded will include 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 will also be entered into the eCRF.

BAL5788 / ceftobiprole medocaril
Clinical Study Protocol
BPR-PIP-001

basilea
PHARMACEUTICA

Version 5.0
21 March 2019

Medication given within 7 days before screening up to the start of ceftobiprole dosing will be recorded as prior medication; if given after the start of ceftobiprole dosing, up to the follow-up safety assessment on Day 7±3, it will be recorded as concomitant.

5 SCHEDULE OF ASSESMENTS AND PROCEDURES

5.1 Summary schedule of assessments

Table 2 presents a summary of the assessments to be performed from screening to the final post-treatment visit.

Table 3 presents a more detailed summary of the assessments and PK sampling times to be performed on Day 1.

5.1.1 Screening (Days −1 to 1)

A parent or legally acceptable representative must provide written informed consent for a subject to participate in the study before any study-specific procedures are carried out.

Informed consent must be obtained within 3 days prior to dosing on Day 1. Once written informed consent is obtained, subjects are considered enrolled in the study.

Subjects in the appropriate Cohort (see Section 3.3) for whom consent has been provided will undergo screening evaluations within 24 hours prior to ceftobiprole dosing. Screening evaluations and dosing may be performed on the same day (Day 1). Laboratory analyses required as part of the screening process which have been performed within the 48 hours prior to ceftobiprole dosing do not need to be repeated, regardless of whether they were performed before or after signing of the ICF.

Screening evaluations (see Table 2) will comprise:

- physical examination
- medical history (within 30 days prior to enrolment)
- review and recording of medication given within the previous 7 days, including systemic antibiotics to be given before and after ceftobiprole dosing
- safety laboratory tests (haematology, clinical chemistry, and urinalysis; see Section 5.2.3.2)
- review of enrolment criteria to ensure subject eligibility, including laboratory test results
- vital signs, body weight and height

Physical examination results and body weight obtained during the screening evaluation do not need to be repeated as Day 1 assessments if they were performed within 6 hours prior to dosing on Day 1.

Table 2 Schedule of assessments

	Screening Day −1 to 1	Dosing Day 1	Follow-up Day 7±3
SCREENING AND ADMINISTRATIVE PROCEDURES			
Written Informed consent[1]	X		
Inclusion/exclusion criteria	X		
Medical history	X		
Prior medications[2]	X		
CEFTOBIPROLE ADMINISTRATION			
Infusion of ceftobiprole[3]		X	
Collection of aliquot of infusion solution[4]		X	
PHARMACOKINETIC PROCEDURES			
Blood sample collection[5]		X	
Urine collection[6]		X	
SAFETY PROCEDURES			
Vital signs[7]	X	X	X
Physical examination	X	X*	X
Body weight and height[8]	X	X*	X
Laboratory tests[9]	X		X
Concomitant medication		X	X
Adverse events		<------------- X ------------->	

[1] Informed consent must be obtained within 3 days prior to dosing on Day 1.
[2] Prior medications administered within the 7 days prior to dosing will be collected.
[3] Ceftobiprole must be administered via a separate infusion line. No other intravenous infusion may be given through the same line during the 4-hour ceftobiprole infusion, and – if feasible – attempts should be made to not simultaneously administer any other antibiotic treatment (i.e., through any infusion line) during the ceftobiprole infusion. If feasible, attempts should be made to allow for a minimum period of 30 minutes between the end of administration of any other antibiotic treatment and the start of ceftobiprole medocaril infusion.
[4] An aliquot of approximately 3 mL of infusion solution will be collected after completion of the ceftobiprole infusion and frozen at below −65 °C immediately after sampling.
[5] Blood samples of 200–300 µL will be obtained for PK analysis at the times described in Table 3.
[6] Attempts should be made to obtain urine at the times described in Table 3; NB: Full portions of urine will be collected from subjects in whom a urinary catheter has been placed for their standard clinical care. Urinary catheters will not be placed for the purpose of the study. For subjects without a urinary catheter, one or more portions of urine may be obtained before, during, and after dosing.
[7] Vital signs (body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) will be measured at the times described in Table 3.
[8] Height must be recorded at screening only. The body weight determination on Day 1 will be used for dose calculation and should be obtained within 6-hours prior to dosing.
[9] Safety laboratory tests include haematology, biochemistry, and urinalysis (see Section 5.2.3.2).
*Physical examination and body weight obtained during the screening evaluation do not need to be repeated as Day 1 assessments if they were performed within 6 hours prior to dosing on Day 1.

Table 3 Schedule of PK sampling and vital signs on Day 1

Time	Vital signs	Blood samples	Urine collection*	Infusion solution aliquot collection
−2 to 0 h			X	
−15 min	X			
Pre-dose		X		
0 to 2 h			X	
1 h	X			
2 h		X		
2 h 15 min	X			
2 to 4 h			X	
4 h (end of infusion)		X		X
4 to 8 h			X	
6 h	X	X		
8 h		X		
8 to 12 h			X	
12 h		X		

* <u>NB</u>: Full portions of urine will be collected from subjects in whom a urinary catheter has been placed for their standard clinical care. Urinary catheters will not be placed for the purpose of the study. For subjects without a urinary catheter, one or more portions of urine may be obtained before, during, and after dosing.

5.1.2 Ceftobiprole dosing (Day 1)

The ceftobiprole dose should be scheduled so that the infusion and subsequent assessments (see Table 3) do not conflict with the ongoing therapy with systemic antibiotics, or routine care.

Ceftobiprole medocaril must be reconstituted and diluted for intravenous (i.v.) administration as described in Section 6.2. Briefly, a single infusion of ceftobiprole medocaril will be given at 7.5 mg/kg (calculated as ceftobiprole mg equivalents; see Section 6.1), in a weight-adjusted volume of infusion solution given as a constant rate over 4 hours. The date and exact start and stop times of the infusion will be entered into the eCRF.

Ceftobiprole must be administered via a separate infusion line. No other intravenous infusion may be given through the same line during the 4-hour ceftobiprole infusion, and – if feasible – attempts should be made to not simultaneously administer any other antibiotic treatment (i.e., through any infusion line) during the ceftobiprole infusion. If feasible, attempts should be made to allow for a minimum period of 30 minutes between the end of administration of any other antibiotic treatment and the start of ceftobiprole medocaril infusion. Body weight measured on Day 1 will be used for dose calculation and should be obtained within 6 hours prior to dosing.

Blood samples (200–300 µL) and urine (if possible) for PK analysis will be collected and prepared (see Sections 5.2.2.1 and 5.2.2.2, respectively), at times described in Table 3.

A physical examination will be performed on Day 1 and body weight will be obtained, unless physical examination and body weight were obtained during the screening evaluation within 6 hours prior doing on Day 1.

Vital signs will be recorded at times described in Table 3.

After completion of the ceftobiprole infusion, an aliquot of approximately 3 mL of infusion solution will be collected and sent for analysis as described in Appendix 2.

Changes in medication will be recorded. Adverse events will be monitored and recorded continuously throughout the study (see Table 2 and Section 5.2.3.1).

5.1.3   Follow-up assessment (Day 7±3)

Each subject will be evaluated for safety on Day 7 ± 3 after ceftobiprole dosing. Safety assessments will comprise physical examination, vital signs, safety laboratory tests (haematology, clinical chemistry, and urinalysis; see Section 5.2.3.2), and AEs.

5.2   Study procedures

5.2.1   Efficacy

The efficacy of ceftobiprole will not be assessed in this study.

5.2.2   Pharmacology

5.2.2.1 Collection and preparation of blood samples

Blood samples of 200–300 µL will be obtained for PK analysis at the times described in Table 3.

The date and exact times of blood sampling will be entered into the eCRF.

Blood for PK analysis should preferably be collected from a vein in the contralateral arm to that used for the i.v. administration of ceftobiprole; however collection may be at any site other than the infusion site, including heel prick sampling or collection through a central line, if available.

Blood samples will be immediately transferred into pre-chilled tubes containing citric acid and EDTA as a coagulant. Samples will be centrifuged, and the supernatant will be frozen and kept at below −65 °C until shipment. Frozen samples will be shipped to the sponsor as described in Appendix 2.

Details on handling of PK samples are provided in the Pharmacokinetics Manual for this study (provided separately).

5.2.2.2 Collection and preparation of urine samples

Attempts should be made to obtain urine at the times described in Table 3.

Full portions of urine will be collected in subjects in whom a urinary catheter has been placed for their standard clinical care. For more details see the Pharmacokinetics Manual

for this study (provided separately). Urinary catheters will not be placed for the purpose of the study.

In subjects without a urinary catheter one or more portions of urine may be obtained at any time during the periods indicated in Table 3, and the date and exact time of sample collection will be entered into the eCRF. The total amount of collected urine should be stabilized with citric acid, frozen and kept at below −65 °C until shipment. Frozen urine should be shipped to the sponsor as described in Appendix 2. For details see the Pharmacokinetics Manual for this study (provided separately).

5.2.2.3 *Analysis of ceftobiprole concentrations*

Plasma and urine concentrations of ceftobiprole medocaril, ceftobiprole, and of the open-ring metabolite (BAL1029), will be quantified by means of a validated liquid-chromatography/ tandem mass spectrometry (LC-MS/MS) method.

5.2.2.4 *Pharmacokinetic parameters*

Plasma and urine samples will be analysed for concentrations of ceftobiprole, and if applicable for concentrations of ceftobiprole medocaril and the open-ring metabolite (BAL1029). The analysis will 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 will be prepared in blank and pre-tested human plasma or urine, and will be subject to the same assay procedure as experimental samples. The limit of quantification (LOQ) will be defined as the lowest concentration of analyte in a human plasma or urine sample, which can be quantitatively determined with inter-assay precision and accuracy of $100 \pm 20\%$. Lower concentrations will 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 subject cohort, if $< 50\%$ of samples are BLQ, drug levels in these samples will be set to zero. If $\geq 50\%$ of samples are BLQ, no mean value will be calculated.

Time-concentration profiles of ceftobiprole in plasma will be analysed by use of non-compartmental models. Actual sampling times will be used in all calculations. The following PK parameters will be determined for each individual, cohort, and by post-natal age:

C_{max}	The observed maximum plasma concentration.
$t_{1/2}$	The apparent terminal elimination half-life, calculated by $t_{1/2} = \ln2/\beta$, where β is the elimination rate constant, estimated by linear least squares regression of the plasma concentration versus time data in the terminal elimination phase.
AUC_{0-t}	The area under the plasma concentration-time curve from time zero to the last sampling time with a concentration above the LOQ. AUC_{0-t} will be calculated according to the linear trapezoidal rule.
$AUC_{0-\infty}$	The area under the plasma concentration-time curve from time zero to infinity, estimated from $AUC_{0-t} + C_t/\beta$, where t is the last sampling time with a concentration above the LOQ.
CL_S	The total systemic clearance, estimated by $CL_S = dose/AUC_{0-\infty}$.
V_{SS}	The apparent volume of distribution at steady state, estimated by $V_{SS} = (dose \times AUMC/AUC^2) - (dose \times T/2AUC)$, where AUMC is the area under the first moment curve and T is the infusion

	time.
T > MIC	The length of time plasma concentrations of ceftobiprole exceed the MIC (4 µg/mL).

Concentrations of ceftobiprole, ceftobiprole medocaril, and open-ring metabolite (BAL1029) in urine will be determined; these results will be analysed by use of descriptive statistics. If a sufficient number of samples are available, parameters of urinary excretion may be determined.

The relationship between exposure (C_{max} and AUC), derived PK parameters (CL_S, V_{SS}, $t_{1/2}$) gestational age, post-natal age, body weight, body mass-index, body surface area, and calculated creatinine clearance will also be assessed.

5.2.3 Safety

The investigator will evaluate subject safety by AE monitoring, physical examination, vital signs and safety laboratory tests (see Table 2).

5.2.3.1 Adverse event monitoring

All AEs occurring from the start of first study medication (Day 1) must be documented as an AE, regardless of whether the event is considered to be related to the study drug or not (see Section 7.1.1).

If possible, a diagnosis should be documented rather than signs and symptoms. All AEs should be recorded in the English language. The investigator should consider whether reports from the parents, legally acceptable representatives or caregivers should be recorded as AEs.

Subjects who withdraw because of a drug-related AE should be followed up until recovery. Adverse events will be recorded throughout the study, from the start of first study medication (Day 1) to the final assessment at follow-up. Reporting of SAEs is described in Section 7.2.2.

5.2.3.2 Laboratory tests

Blood and urine samples obtained at screening and at the follow-up evaluation on Day 7±3 will be analysed for the following safety laboratory parameters:

Haematology:	Haematocrit, red blood cell (RBC) count, total and differential white blood cell (WBC) count, platelet count, and reticulocyte count.
Blood chemistry:	Aspartate aminotransferase (AST) alanine aminotransferase (ALT), total bilirubin, creatinine, sodium, chloride and potassium.
Urinalysis:	Dipstick for pH, glucose[*], blood[*], and protein.[*]
	([*]Microscopic examination of sediment if positive)

The choice of site and procedure for blood draws (e.g., venous site or heel-prick, or through an existing arterial line) will be made by the investigator depending on the availability of access, the volume of blood required, and the type of laboratory test to be done. Blood draws should be performed according to standard procedures of the institution.

The anticipated volume of blood required for PK assessment will be approximately 1.2 mL to 1.8 mL (6 sampling time points, see Table 3, with a blood volume of 200–300 µL per sample).

5.2.3.3 Physical examination

Each subject will undergo a physical examination at screening, on Day 1 and at the follow-up assessment on Day 7±3. Abnormalities will be described in the eCRF.

Physical examination and body weight obtained during the screening evaluation do not need to be repeated as Day 1 assessments if they were performed within 6 hours prior to dosing on Day 1.

5.2.3.4 Vital signs

Vital signs will include body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures. Vital signs will be measured at the times described in Table 2 and Table 3, and results will be entered into the eCRF.

Note: Body temperature may be measured either axillary, orally, rectally, tympanic or skin temperature (e.g. by a patch); however, for each subject only one method should be used consistently throughout the entire study.

6   STUDY DRUGS

6.1   Dose and schedule

Subjects will receive a single infusion of ceftobiprole medocaril, given in a weight-adjusted volume at a constant rate over 4 hours. The dose will be 7.5 mg/kg, calculated as ceftobiprole equivalents (7.5 mg ceftobiprole corresponds to 10.0 mg ceftobiprole medocaril sodium).

Ceftobiprole must be administered via a separate infusion line. No other intravenous infusion may be given through the same line during the 4-hour ceftobiprole infusion, and – if feasible – attempts should be made to not simultaneously administer any other antibiotic treatment (i.e., through any infusion line) during the ceftobiprole infusion. If feasible, attempts should be made to allow for a minimum period of 30 minutes between the end of administration of any other antibiotic treatment and the start of ceftobiprole medocaril infusion.

As described in Section 3.3, subjects will be assigned to 3 cohorts on the basis of gestational age, and further stratified by post-natal age. The 3 cohorts will be dosed sequentially. Subjects in Cohorts 2 and 3 may not be dosed until at least 5 subjects from the previous cohort have received their full planned dose and undergone the follow-up safety evaluation (Day 7±3).

Before initiation of dosing in Cohort 2 and Cohort 3, available safety data from subjects in the previous cohort will be made available to all investigators, and the decision to initiate dosing in a new cohort will be made jointly by the sponsor and the investigators.

6.2   Administration

Details on study drug preparation and administration are described in the Study Drug Administration Manual (provided separately). Sterile technique will be used in all stages of preparation. Procedures can be briefly summarized as follows:

a) Ceftobiprole medocaril will be supplied in vials containing 500 mg ceftobiprole (corresponding to 667 mg of ceftobiprole medocaril) as lyophilized powder.

b) The vial will be reconstituted with 10 mL dextrose 5% to obtain a reconstituted solution of a concentration of 50 mg/mL ceftobiprole.

c) 4 mL (equivalent to 200 mg ceftobiprole) of this reconstituted solution will be further diluted with 46 mL of dextrose 5% in a 50 mL syringe. The final volume in the syringe will be 50 mL, and the concentration of ceftobiprole in that 50 mL syringe will be 4 mg/mL.

d) Depending on the body weight of the subject, the required volume corresponding to a dose of 7.5 mg/kg ceftobiprole will be infused using a calibrated infusion pump device as shown in Table 4. For example, for a child of 1 kg body weight, 7.5 mg ceftobiprole will be administered, corresponding to 1.88 mL of the 4 mg/mL ceftobiprole solution. The infusion rate for a 4-hour infusion is therefore 0.47 mL/h.

Table 4   Ceftobiprole administration and dose calculation by body weight

Body weight (kg)	Ceftobiprole single dose (mg)	Required volume in mL of the reconstituted ceftobiprole solution (50 mg/mL)	Required volume of dextrose 5 %	Total syringe volume	Volume of the final solution for infusion administered from the 50 mL syringe	Infusion rate (mL/h)
0.7	5.25	4 mL	46 mL	50 mL	1.31 mL	0.33
0.8	6	4 mL	46 mL	50 mL	1.50 mL	0.38
0.9	6.75	4 mL	46 mL	50 mL	1.69 mL	0.42
1	7.5	4 mL	46 mL	50 mL	1.88 mL	0.47
1.2	9	4 mL	46 mL	50 mL	2.25 mL	0.56
1.5	11.25	4 mL	46 mL	50 mL	2.81 mL	0.70
1.8	13.5	4 mL	46 mL	50 mL	3.38 mL	0.84
2	15	4 mL	46 mL	50 mL	3.75 mL	0.94
2.5	18.75	4 mL	46 mL	50 mL	4.69 mL	1.17
3	22.5	4 mL	46 mL	50 mL	5.63 mL	1.41
3.5	26.25	4 mL	46 mL	50 mL	6.56 mL	1.64
4	30	4 mL	46 mL	50 mL	7.50 mL	1.88
4.5	33.75	4 mL	46 mL	50 mL	8.44 mL	2.11
5	37.5	4 mL	46 mL	50 mL	9.38 mL	2.34
5.5	41.25	4 mL	46 mL	50 mL	10.31 mL	2.58
6	45	4 mL	46 mL	50 mL	11.25 mL	2.81
6.5	48.75	4 mL	46 mL	50 mL	12.19 mL	3.05
7	52.5	4 mL	46 mL	50 mL	13.13 mL	3.28
7.5	56.25	4 mL	46 mL	50 mL	14.06 mL	3.52
8	60	4 mL	46 mL	50 mL	15.00 mL	3.75

Body weight used for dose calculation will be obtained on Day 1 within 6 hours prior to dosing.

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

Only dextrose 5% is permitted for reconstitution and dilution. Once ceftobiprole in the vial has been reconstituted with 10 mL of dextrose, further dilution of the 4 mL from the reconstituted solution with 46 mL of dextrose 5% (to obtain a 50 mL syringe with a concentration of 4 mg/mL) must be completed within 1 hour.

The final solution for infusion in the 50 mL syringe is chemically and physically stable under the following conditions:

- 24 hours in a refrigerator (2–8 °C) followed by 12 hours at room temperature
- 12 hours at room temperature

The infusion therefore must be completed within these time limits. Reconstituted and infusion solutions must 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.

Further details of ceftobiprole administration are described in the Study Drug Administration Manual (provided separately).

After the end of the ceftobiprole infusion, a 3-mL aliquot of the drug infusion solution will be collected for analysis of ceftobiprole concentration (see Appendix 2). The 3-mL aliquot must be frozen at below −65 °C.

6.3 Blinding and randomization

This is an open-label study. Subjects will not be randomized, but will be enrolled and assigned to 3 cohorts on the basis of gestational age, and further stratified by post-natal age (see Section 3.3). Cohorts will be dosed sequentially, starting with higher gestational age (see Section 3.3). As described in Section 6.1, the decision to start dosing in Cohorts 2 and 3 will be made jointly by the sponsor and the investigators after review of safety data and PK data from at least 5 subjects in the previous cohort.

6.4 Packaging and labelling

Study drug vials will be supplied by the sponsor to the investigator. The sponsor will ensure that the study medication and certificates of analysis are available before the start of the study.

Study drug for i.v. administration will be presented as vials of sterile lyophilized ceftobiprole medocaril (BAL5788) containing the equivalent of 500 mg ceftobiprole. The lyophilisate will be stored in a refrigerator (2 °C – 8 °C).

The study drug vial labels will identify the sponsor, study number, vial contents, batch number, and expiry date.

Study drug will be kept in a secure location under adequate storage conditions. Further details on handling, preparation, and administration of i.v. ceftobiprole are provided the Study Drug Administration Manual (provided separately).

6.5 Compliance check and accountability

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

A Drug Dispensing Log must be kept current, and should contain the following information:

- the identification of the subject to whom the drug was dispensed (subject number)
- the date(s) and quantity of the drug dispensed to the subject
- the initials of the person who dispensed the drug (pharmacist)
- the initials of the person who administered the drug (nurse)

The inventory must be available for inspection by the Clinical Study Monitor. Drug supplies, including partially used or empty containers and the dispensing logs, must be returned to the Clinical Study Monitor at the end of the study.

When requested in writing by the sponsor, unused drug supplies may be destroyed by the investigator. Records must be maintained by the investigator which show the identification and quantity of each unit disposed of, the method of destruction (taking into account applicable legal requirements), and the person who destroyed the test substance. These records must be submitted to the sponsor.

7 SUBJECT SAFETY

7.1 Adverse events

7.1.1 Definition of adverse events

An AE is any adverse change from the subject's baseline (pre-therapy) medical condition which occurs during the course of a clinical study after test medication has been given, whether considered related to treatment or not. Treatment includes all study drugs administered during the course of the study. Events involving exacerbations or worsening of pre-existing illnesses should be recorded as AEs.

A treatment-emergent AE in this study is defined as any AE occurring between first administration of study drug and the follow-up visit at study Day 7±3. If the last scheduled study visit occurs later than 10 days after stopping the treatment, any AE occurring after Day 10 will be considered non-treatment-emergent unless reassigned based on a medical review conducted by the sponsor prior to database lock.

Adverse medical occurrences that appear between the provision of informed consent and first drug administration will be entered into the Medical History section of the eCRF.

If possible, a diagnosis should be documented rather than signs and symptoms. All AEs should be recorded in the English language.

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. These events are to be entered into the Adverse Events section of the eCRF under the signs, symptoms or diagnoses associated with them.

7.1.2 Evaluation of adverse events

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

Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Moderate: Moderate symptoms; minimal, local or noninvasive intervention indicated

Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; or disabling

The relationship of AEs to the study treatment will be assessed as:

- unrelated
- remotely related
- possibly related; or
- probably related

Appendix 3 provides criteria for relationship assessments.

A causal relationship is suspected for all AEs reported with a relationship of 'possible' or 'probable'.

7.2 Serious adverse events

Any SAE occurring during the course of the study, irrespective of the treatment received by the subject, must be reported to the sponsor or designated safety representative within 24 hours of awareness of the event.

7.2.1 Definition of serious adverse events

An SAE is any AE that at any dose:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject 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 are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. An unexpected AE is an AE the nature or severity of which is not consistent with the applicable product information.

Note: **Death** is considered an outcome of an AE. Whenever possible the underlying cause of death should be reported as the AE.

A **life-threatening AE** is any adverse experience that places the subject at risk of death at the time it occurred, i.e., it does not include an event that, had it occurred in a more severe form, might have caused death.

In-patient hospitalization is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from a medical floor to the coronary care unit, from the neurological floor to the tuberculosis unit).

Preplanned hospitalizations and **elective surgery** which are not due to a worsening or exacerbation of an underlying disease do not constitute an SAE.

7.2.2 Reporting of serious adverse events

Any SAE occurring during the active treatment period or during the protocol-defined follow-up period until the last study visit, whether considered treatment-related or not, must be reported immediately to the sponsor's safety representative listed below. The last study visit in this study will be scheduled on Day 7 ± 3 after stopping the treatment. If the last scheduled study visit occurs later than on Day 7 ± 3 after stopping the treatment, SAEs must be reported until the actual (late) visit date.

Adverse event reporting will not be solicited after the last study visit:

- A serious adverse event (including those resulting in death) that occurs after this time and which is considered related to study drug, should be reported.

- For deaths which occur after the last study visit (until database lock) that are reported unsolicited (related or unrelated to study drug), the date of death will be captured in the eCRF.

- Serious events that are reported unsolicited after the last study visit that are unrelated to study drug will not be collected and will not be reported as serious adverse events.

Safety contact

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** **eFax (US):   +1 866 902 7489**

The Sponsor's safety representative will submit reports for expeditable SAEs to health care authorities and Independent Ethics Committees / Institutional Review Boards (IECs/IRBs) as required by applicable laws and regulations.

The investigator must notify the local IEC/IRB of an SAE in writing in accordance with applicable laws and regulations.

The description of the SAE should be as complete as possible and allow for a medical assessment of the case. At a minimum, the SAE report must contain:

- a subject identifier
- an adverse event description
- action taken with regards to study drug
- outcome information
- the investigator's causality assessment

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

Causality should be rated by the investigator according to Appendix 3 of the protocol.

A causal relationship is suspected for all AEs reported with a relationship of 'possible' or 'probable'.

7.3   Treatment and follow-up of adverse events

The investigator or other physician in attendance will administer therapy as clinically indicated. All SAEs and those AEs for which the relationship to study drug is plausibly related, should be followed up until they have returned to baseline status or stabilized. If a clear explanation is established, it should be entered into the eCRF.

7.4   Laboratory test abnormalities

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be entered into the eCRF. Abnormal laboratory results should be recorded as an AE if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

7.5   Pregnancy

Not applicable.

7.6   Dose modifications for safety reasons

The intended dose may not be modified; however the 4-h infusion may be stopped at the investigator's discretion (see Section 4.4).

7.7   Warnings and precautions

Detailed warnings and precautions are provided in the IB. Serious or significant adverse reactions that may occur in subjects receiving β-lactam antibiotics include hypersensitivity (anaphylaxis), *Clostridium difficile* associated diarrhea/ pseudo-membranous colitis, superinfections of non-susceptible organisms, precipitation when co-administered through the same infusion line with calcium-containing solutions, and seizures.

8 STATISTICAL CONSIDERATIONS

8.1 Primary and secondary study variables

The primary study variables are PK parameters C_{max}, $AUC_{0-\infty}$ and $T > MIC$ (presuming an MIC of 4 µg/mL).

Secondary variables comprise other PK parameters (see Section 5.2.2.4), and safety variables as described in Section 5.2.3.

8.2 Statistical and analytical methods

8.2.1 Statistical model

Plasma concentrations at each time point of measurement will be evaluated by descriptive statistics, including arithmetic mean, standard deviation (SD), minimum, maximum, and median. Actual sampling times will be used to calculate PK parameters. If $\leq 50\%$ of the values at a given time point are BLQ, these values will be set to zero for mean value calculation. If more than 50% of the values at a given time point are BLQ, no mean value will be calculated. Mean plasma concentration profiles of each cohort will be generated according to these criteria.

For PK evaluation, BLQ-values at infusion start will be set to zero, BLQ-values at the end of the sampling period will be disregarded for PK assessment. Single BLQ values during blood sampling will be taken as 'missing values', if the following sample(s) show a concentration above the BLQ value.

8.2.2 Sample size calculation

No sample size calculation has been performed for this study. Study drug treatment of 15 subjects per dosing cohort (total $N = 45$), is based on experience and is considered sufficient to fulfil the objectives of this study.

8.2.3 Hypothesis testing

No formal hypothesis testing will be performed.

8.2.4 Statistical analyses

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

Pharmacokinetic parameters will be presented by individual listings and descriptive summary statistics including arithmetic and geometric means, arithmetic and geometric coefficients of variation, standard deviation, minimum, median, and maximum.

Adverse events will be listed by individual subject and by frequency tables broken by body system. Vital signs will be listed and summarized by means and standard deviations. Laboratory test values will be presented in individual subject listings with flagging of values outside the normal ranges and marked normal ranges, by frequency tables for each parameter showing the numbers of subjects with values outside normal ranges and marked normal ranges, and by shift tables for each parameter showing the numbers of subjects with adverse changes from baseline.

Subjects may be excluded from the PK analysis if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol or if data are unavailable which may influence the PK analysis. All subjects who receive any amount of study medication will be included in the analysis of safety. Subjects excluded from any analysis will be listed along with the reasons for exclusion.

8.2.5 Interim analysis

No hypothesis-testing interim analysis is planned. PK data from early dosing cohorts may be analysed before dosing in later cohorts is started or completed. Safety data will be reviewed on an ongoing basis.

9 DATA QUALITY ASSURANCE AND VERIFICATION PROCEDURES

9.1 Electronic case report forms

An electronic data capture (EDC) system is used to collect the data in this study. The EDC system provides functionality for the clinical sites to enter the data directly into the eCRFs and respond to data discrepancies. Once the data are entered, the information is encrypted and transmitted over the Internet to a clinical trial server, where it is electronically reviewed. Any resulting data queries are immediately sent back to the site for resolution.

The system automatically keeps a full audit trail of all data changes that occur. The clinical team will undertake additional manual review of the data, but all resulting data queries or clarifications will be entered into the EDC system for resolution. All eCRFs will be completed according to instructions provided in the eCRF Completion Guidelines and ICH GCP guidelines.

10 PROTOCOL AMENDMENTS

Substantial protocol amendments must be prepared by the Sponsor and be reviewed and approved by the Project Physician.

Protocol amendments must be submitted to the appropriate IEC or IRB for information and approval in accordance with applicable requirements, and to regulatory authorities if required. Approval must be awaited before any changes are implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or changes involving only logistical or administrative aspects of the study (e.g., changes to monitors, telephone numbers etc.

11 PREMATURE TERMINATION OF THE STUDY

The sponsor reserves the right to terminate the study at any time, and an investigator has the right to terminate his or her participation to the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the sponsor and the investigator must ensure that adequate consideration is given to the protection of the subject's interests.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Good Clinical Practice

The study will be conducted in accordance with the ICH Tripartite Guideline E6 *Guideline for Good Clinical Practice* [7] and applicable regulatory requirements.

12.2 Informed consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable under local regulations), to obtain prior written informed consent from the subject's parent(s) or legally acceptable representative 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 legally acceptable representative that they are completely free to refuse consent for the infant to enter the study, and to withdraw the infant 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 site.

If the parent(s) or legally acceptable representative 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 legally acceptable representative 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 legally acceptable representative.

The eCRFs 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 legally acceptable representatives 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.

12.3 Subject confidentiality and data protection

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. This includes any electronic data generated during the study. In the eCRFs or on other documents submitted to the sponsor, subjects must not be identified by their names, but by an identification code. The investigator must keep a confidential subject identification code list as described in ICH GCP §8.3.21, and must ensure that all local data protection laws are respected.

12.4 Independent Ethics Committees / Institutional Review Boards

This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent), as well as any advertising or compensation given to the subject, will be submitted to an IEC/IRB.

Approval from the IEC/IRB must be obtained before starting the study, and should be documented specifying the date on which the committee met and granted approval.

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

12.5 Study records

The investigator 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.

12.5.1 Investigator's Study File

The Investigator's Study File will contain all essential documents as required by ICH E6, e.g., the protocol/amendments, pdf of eCRF with audit trail, IEC/IRB and governmental approval with correspondence, sample informed consent forms, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

12.5.2 Subject source documents

Subject source documents used to record key efficacy/safety parameters independent of the eCRFs may include for example subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrolment logs.

12.5.3 Electronic case report forms

For each subject enrolled, an eCRF must be completed and signed off electronically by the investigator or authorized sub-investigator. This also applies to records for those subjects who fail to complete the study (even during a screening period if an eCRF was initiated). If a subject is withdrawn from the study, the reason must be entered into the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

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

12.5.4 Document retention and archiving

The 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 investigator when the study documents can be destroyed, subject to local regulations.

Should the 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 investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, arrangements must be made between the investigator and the sponsor for appropriate storage.

13 MONITORING

13.1 Monitoring

The study monitor will visit the investigator and the study facilities on a regular basis throughout the study to verify the adherence to GCP, the protocol and the completeness, consistency and accuracy of the data being entered into the eCRFs.

13.2 Source data verification

The investigator must ensure that the monitor has direct access to all required study data (source documents) during the regular monitoring visits. This includes all subject records needed to verify the entries in the eCRFs.

14 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. The study may also be inspected by health authority inspectors, after appropriate notification. In the event of an audit or an inspection, the investigator must ensure that direct access to all study documentation, including source documents, will be granted to the auditors or inspectors.

15 PUBLICATION POLICY

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 have to 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 the investigator. 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 will be determined by mutual agreement.

16 REFERENCES

1. Curtis C, Shetty N. 2008. Recent trends and prevention of infection in the neonatal intensive care unit. Curr Opin Infect Dis 21: 350–356.

2. Strunk T et al. 2013. Genetic and epigenetic susceptibility to early life infection. Curr Opin Infect Dis doi: 10.1097/QCO.0b013e32835fb8d9.

3. Blumer JL et al. 1995. Sequential, single-dose pharmacokinetic evaluation of meropenem in hospitalized infants and children Antimicrob Agents Chemother 39 : 1721–1725.

4. Zingg W et al. 2008. Healthcare-associated infections in neonates. Curr Opin Infect Dis 21: 228–234.

5. Parker EM et al. 1995. The pharmacokinetics of meropenem in infants and children: a population analysis. Antimicrob Agents Chemother 36 (Suppl A) : 63–71.

6. Clinical Study Report 30982081-CSI-1006 (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. Protocol 30982081-CSI-1006.

7. ICH Tripartite Guideline E6, "Guideline for Good Clinical Practice" (July 1996).

8. Clinical Study Report 30982081-CSI-1004 (31 January 2006). An open-label, pharmacokinetic study of single and multiple intravenous infusions of ceftobiprole 500 mg administered to healthy, adult subjects (Protocol 30982081-CSI-1004).

9. Nonclinical Research Report for Study 901275 (12 November 2008). Ceftobiprole medocaril (BAL5788): A subcutaneous toxicity study in neonatal and juvenile albino rats (TOX8611).

BAL5788 / ceftobiprole medocaril
Clinical Study Protocol
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Version 5.0
21 March 2019

17   APPENDICES

Appendix 1   Rationale for dose selection (neonates / paediatric population ≤ 3 months of age)

Overview of dosing rationale

The dose selected for this study is 7.5 mg/kg as a single-dose 4-hour infusion.

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

1. The level of drug exposure that have been demonstrated to be effective in treating nosocomial pneumonia and community-acquired pneumonia in adults
2. The PK and safety results of a previous single-dose study in paediatric subjects aged ≥ 3 months to < 18 years (study CSI-1006)
3. The AE profile of ceftobiprole in adults
4. The results of a toxicity study in juvenile animals
5. Pharmacokinetic modeling results
6. The experience in the paediatric population with other beta-lactams

Target drug exposure and efficacy considerations

Ceftobiprole is a cephalosporin and belongs to the β-lactam class of antibiotics. For β-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[1]. 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[2] and in the Phase 3 studies in nosocomial pneumonia (BAP248/307)[3] and in community-acquired pneumonia (CAP-3001)[4].

Accordingly, considering that ceftobiprole will be used as a broad-spectrum antibiotic, a dosing regimen resulting in 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.

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[1] Craig. Does the dose matter? Clin Infect Dis 2001;33:233–237
[2] Craig. *In vivo* pharmacodynamics of ceftobiprole against multiple bacterial pathogens in murine thigh and lung infection models. *Antimicrob Agents Chemother* 2008; 52:3492–3496
[3] Muller. %*ft.*>MIC predicts probability of clinical outcome in the treatment of nosocomial pneumonia by ceftobiprole. ECCMID 2013 Poster P904
[4] 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 h with limited accumulation after repeated every 8-hour (q8h) administration. The PK 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 AEs being dysgeusia, nausea and vomiting. In pooled safety data from two 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 C_{max} 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 q8h 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 ceftobiprole medocaril/kg/day [9]. The corresponding exposures are summarized in Table 5.

Table 5   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

Human experience in the paediatric population

Study CSI-1006 evaluated the PK 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 four 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 PK evaluable subset, ceftobiprole volume of distribution and systemic clearance increased with age and reached almost healthy-adult historical values in the 12 to < 18 years age group [6].

At the doses administered in study CSI-1006 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 PK 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., PD target of 62.3%–90.1% was achieved [8].

However, at the doses investigated, in each age group there were children underexposed in terms of PD target and notably in the age group of > 3 months – < 2 years [IB, 6]. Observed PK and PD parameters corrected by the free fraction in the age group > 3 months - < 2 years are presented in Table 6.

Table 6   Observed pharmacokinetic and pharmacodynamics parameters corrected by the free fraction in the age group > 3 months to < 2 years (N=16)

Ceftobiprole dose administered: 15 mg/kg 2-h infusion (single dose)	
$T_{1/2}$ (h)	2.1 (1.1–4.1)
fC$_{max}$ (µg/mL)	18.9 (8.22–41.2)
fAUC$_{0-8h}$ (µg.h/mL)	60.4 (25.2–124)
fT>MIC = 4 µg/mL (h)	5.3 (2.8–7.5)
Number of subjects below the target of 50% of dosing interval	2 out of 16

The safety profile observed in study CSI-1006 after single-dose administration of ceftobiprole (7 mg/kg to 15 mg/kg) was generally similar to that observed in adults. No new or unexpected safety signals associated with study drug were observed. 31 subjects (48%) reported at least one 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.

Pharmacokinetic modeling

The modeling strategy was to optimize the dosing regimen (dose, dosing interval and infusion duration) for paediatric subjects > 3 months to < 2 years in order to maximize fT>MIC=4 µg/mL and maintain exposure in the range well tolerated by adults, and below the exposure at the NOAEL in the juvenile rat study [9] 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 dosing regimen for the age group of ≥ 3 month to < 2 years was 20 mg/kg as a 4-h infusion q8h from an exposure/PD and safety point of view as summarized in Table 7. Exposure in this age group at the recommended dose of 20 mg 4-h infusion q8h is 2 to 3-fold lower than the exposure obtained at the NOAEL in the juvenile toxicity study for Day 1 post-partum pups.

Table 7   Predicted exposure to ceftobiprole in the age group ≥ 3 months to < 2 years

Number of subjects (N=16)	
Ceftobiprole dose of 20 mg/kg 4-h infusion q8h	
fT>MIC=4 μg/mL below 50% of dosing interval	0
Above highest adult C_{max}	0
Above highest adult AUC	1
Above exposure (C_{max} and AUC) at NOAEL	0

A PK model developed for neonates and infants was based on the fact that ceftobiprole is eliminated by the kidneys, and approximately 90% of the dose is recovered unchanged in urine, distribution is restricted to the extracellular compartment, and the systemic clearance of ceftobiprole correlated (coefficient of correlation of 0.9858) with the creatinine clearance in a dedicated clinical pharmacology study in renally impaired subjects. The model provided estimates for exposure and urinary concentration presented in Table 8.

Table 8   Estimated normal and worst-case exposure and urinary concentrations following a single dose of 7.5 mg/kg ceftobiprole in neonates and infants up to a postnatal age of 3 months.

PNA	Dose (mg)	Normal condition			Worst-case			Dose (mg /h)	Urine output (mL/h)	Urine conc. (mg/ mL)
		S_{cr} (mg/dL)	$T_{1/2}$ (h)	AUC (μg.h/ mL)	S_{cr} (mg/dL)	$T_{1/2}$ (h)	AUC (μg.h/ mL)			
8 d	25.7	0.38	2.3	63.2	1.10	10	189.3	6.4	7	0.94
15 d	27.4	0.35	2.2	60.5	1.10	11	189.8	6.9	7	0.94
1 mo	30.5	0.28	1.9	50.5	0.88	9	157.1	7.6	8	0.94
2 mo	37.7	0.25	1.9	51.6	0.88	10	182.5	9.4	10	0.94
3 mo	44.0	0.23	1.6	42.8	0.88	9	166.5	11.0	12	0.94

PNA = postnatal age; S_{cr} = serum creatinine; $T_{1/2}$ = half-life; AUC = area under the curve

Experience in paediatric subjects with other β-lactams

Numerous PK studies and population PK/PD analysis in paediatric subjects and neonates were conducted with meropenem. Depending on the infusion duration (0.5 h to 4 h) doses of 20 mg/kg to 40 mg/kg were predicted to be efficacious in full-term and pre-term neonates[5,6,7]. These doses are similar to those investigated in infants with age > 2 months.

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[5] Padari. Short versus long infusion of meropenem in very-low-birth-weight neonates. *Antimicrob Agents Chemother.* 2012;56:4760-4

The present study will include full-term neonates and pre-term neonates. The creatinine clearance is reduced in pre-term neonates[8]. Therefore, a conservative approach is taken and a dose of 7.5 mg/kg 4-h infusion will be investigated in neonates and children age 3 months or below. This dose level of 7.5 mg/kg is considered to provide an adequate safety margin for subjects whose renal excretion capacity may be limited, and will allow for appropriate dose modeling to determine whether further dose stratification is required within the various groups of neonates, e.g. based on gestational or post-natal age, body weight, body surface area, creatinine clearance or other covariates.

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[6] Bradley. Meropenem pharmacokinetics, pharmacodynamics, and Monte Carlo simulation in the neonate. *Pediatr Infect Dis J.* 2008;27:794-9

[7] Ohata. Optimal dosage regimen of meropenem for pediatric patients based on pharmacokinetic/ pharmacodynamic considerations. *Drug Metab Pharmacokinet.* 2011;26(5):523-31

[8] van den Anker. Meropenem pharmacokinetics in the newborn. *Antimicrob Agents Chemother.* 2009;53(9):3871–9

Appendix 2   Collection, storage, and shipping of blood, plasma, infusion solution, and urine for pharmacokinetic analyses

Details on handling of PK samples are provided in the Pharmacokinetics Manual for this study (provided separately). The Pharmacokinetics Manual also contains instructions on shipping samples, including transport logistics. Materials needed for sampling will be provided by the sponsor.

Preprinted labels for blood, plasma, urine, and infusion solution collection tubes will be supplied by the sponsor. They will include the protocol number, matrix (coded by label color), subject number, planned time of collection. Labels should be fixed lengthwise to room-temperature tubes, with the colored portion at the bottom of the tube. DO NOT place any tape around the label; the labels are designed to stick without the use of tape. The actual date and clock sampling times should be entered into the eCRFs. All tube labels should be in indelible ink (ball-point pen).

Blood collection

Blood samples will be collected and transferred immediately into pre-chilled tubes containing 2M citric acid. Exposure to direct sunlight should be avoided.

Plasma preparation

As soon as possible, but not later than 30 minutes after blood collection, plasma should be separated from blood cells by centrifugation in a refrigerated centrifuge (approximately +4 °C). The plasma supernatant should be transferred immediately into a labeled tube and stored below −65 °C until shipment.

Urine collection

The total amount of urine produced by the subject at the time of collection (if possible) should be transferred into polypropylene collection bottles made of light-protecting material; exposure of urine samples to sunlight should be avoided. The urine collection bottles will be adjusted after collection with 2M citric acid. The pH should be between 4.0 and 5.5. Samples will be stored below −65 °C until shipment.

Infusion solution collection

An aliquot of infusion solution will be collected after completion of the infusion, transferred to a tube, and stored below −65 °C until shipment.

Shipping

Plasma, urine, and infusion solution samples should be shipped in an upright position on dry ice.

Frozen samples will be shipped to:
Swiss BioQuant AG
c/o ███████████████
Kägenstrasse 18
CH-4153 Reinach, Switzerland
Tel: ██████████
Fax ██████████

E-mail: ████████████████████

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Appendix 3 Criteria for evaluating relationship between adverse events and study treatment

UNRELATED

This category is applicable to an AE that meets the following 3 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.

REMOTE

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 re-appear.

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 "unrelated" or "remote", nor the criteria for "probable". An AE would be considered possible if, or when, for example:

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 3 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 re-appear.

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 will be regarded as strong evidence of probable relationship to study drug.

Appendix 4   Laboratory reference values and formulas

Impaired renal function or known significant renal disease, as evidenced by an estimated glomerular filtration rate

Kidney maturation in the neonate has been described in two European guidance documents. [9],[10] The key points are:

- Glomerular filtration matures faster than the tubular function. Both depend not only on age and maturational status but also on adverse factors occurring in the pre- and post-natal period, including for example intrauterine growth retardation or administration of nephrotoxic drugs to the mother and the neonate.

- Post-menstrual age (PMA) (gestational age [GA] + postnatal age) of the neonate is likely to be the best parameter of the ongoing neonatal maturation

  - There may be two-fold to four-fold difference in GFR values between premature and full-term newborns.

  - From 26 weeks of GA at birth to 34 weeks of PMA, the increase in GFR is limited because of incomplete nephrogenesis.

  - Birth triggers a dramatic increase in GFR. The GFR increases from 10 mL/min/1.73 m^2 at birth to 20 to 30 mL/min/1.73 m^2 after 2 weeks.

  - After the first month, serum creatinine remains stable during the first 2 years of life (under 44 μMol/L = 0.5 mg/dL in the full-term neonate).

- Serum creatinine is elevated in the first days of life reflecting maternal creatinine and a low intrinsic GFR.

- In premature neonates, the persistence of an elevated serum creatinine during the first weeks of life is the result of a transitory process of tubular creatinine reabsorption.

- To monitor renal function serum creatinine is used after the first week of life in full-term neonates and after 4 weeks in premature neonates. Before these times, intra-individual changes (related to post-menstrual age) in serum creatinine are used as a guide to renal function.

In addition, the following references must be considered:

- Schwartz[11] published the following modified formula (based on creatinine levels determined with the enzymatic method):

  eGFR (mL/min/1.73m^2) = 0.413 • length (cm) / creatinine (mg/dL)

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9   EMA (2004) Discussion paper on the impact of renal immaturity when investigating medicinal products intended for paediatric use

10   CHMP, PDCO (2009) Guideline on the investigation of medicinal products in the term and preterm neonate

11   Schwartz GJ, et al (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–37

- Laboratory normal ranges (enzymatic method):

	Creatinine (mg/dL)	
UZ Leuven	0.31 – 0.88 (< 1 month)	0.16 – 0.39 (1–12 months)
AZ Sint-Jan	0.24 – 0.85 (< 2 month)	0.17 – 0.42 (2–12 months)

Abitbol[12] reported creatinine levels of 0.68 ± 0.14 mg/dL during postnatal day 3–7 in 60 preterm infants (34 ± 3 weeks). The same report presented a graph of eGFRs calculated with the modified Schwartz formula, in which the values of all age groups were greater than 20 mL/min/ 1.73 m^2. Of note, the creatinine-based equation underestimated the GFR compared to the CysC-based equations, especially in preterm neonates.

- In the meropenem PK study published by Van den Anker[13], a creatinine level of greater than 140 µmol/L (= 1.58 mg/dL) led to the exclusion of the subject from the study.

- Two graphs presented at an EMA Workshop on regulatory and scientific issues related to the investigation of medicinal products intended for neonate use[14] indicated that creatinine levels in neonates of more than 1000 g body weight, or a GA of more than 27 weeks, fell from a maximum of about 110 µmol/L on day 1 to about 50 µmol/L within 3 to 4 weeks.

Conclusion

Serum creatinine levels are generally used to monitor renal function.[10] GFR is indirectly proportional to creatinine, i.e. a GFR of 2/3 of normal corresponds to a 1.5-fold higher than normal creatinine level. Since PMA is the best parameter of kidney maturation, the following creatinine thresholds (determined with the enzymatic method) may be used to support the evaluation of exclusion criterion 5:

PMA (weeks)	Creatinine (mg/dL)	Rationale
28–34 completed	1.32	150% of the upper limit of the laboratory normal ranges
35–42 completed	1.1	Arithmetic mean of 1.32 and 0.88
> 42	0.88	Upper limit of the laboratory normal ranges of the lower age groups and slightly more than 150% of 0.5 mg/dL, the stable creatinine level during the first 2 years of life

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[12] Abitbol CL et al (2014) Neonatal kidney size and function in preterm Infants: What is a true estimate of glomerular filtration rate? J Pediatr 164:1026-31).

[13] Van den Anker JN, et al (2009) Meropenem pharmacokinetics in the newborn. AAC 53(9):3871

[14] Van den Anker (2006) Workshop on Regulatory and Scientific Issues related to the Investigation of Medicinal Products intended for Neonatal Use

Considering these creatinine thresholds, a GFR estimated with the modified Schwartz formula of less than the values given below might provide evidence of impaired renal function or known significant renal disease:

Length (cm)	eGFR threshold (mL/min/1.73m^2)		
	Post-menstrual age (weeks)		
	38–34 completed	35–42 completed	> 42
33	10.3	12.4	15.5
34	10.6	12.8	16.0
35	11.0	13.1	16.4
36	11.3	13.5	16.9
37	11.6	13.9	17.4
38	11.9	14.3	17.8
39	12.2	14.6	18.3
40	12.5	15.0	18.8
41	12.8	15.4	19.2
42	13.1	15.8	19.7
43	13.5	16.1	20.2
44	13.8	16.5	20.7
45	14.1	16.9	21.1
46	14.4	17.3	21.6
47	14.7	17.6	22.1
48	15.0	18.0	22.5
49	15.3	18.4	23.0
50	15.6	18.8	23.5
51	16.0	19.1	23.9
52	16.3	19.5	24.4
53	16.6	19.9	24.9
54	16.9	20.3	25.3
55	17.2	20.7	25.8
56	17.5	21.0	26.3
57	17.8	21.4	26.8
58	18.1	21.8	27.2
59	18.5	22.2	27.7
60	18.8	22.5	28.2

Investigators will exercise their clinical knowledge in conjunction with these thresholds when determining the applicability of exclusion criterion 5 to individual patients.