CLINICAL STUDY PROTOCOL

BPR-PIP-003

A multicenter, open-label, single-arm, multiple-dose study to evaluate the safety, pharmacokinetics, and efficacy of ceftobiprole medocaril in term and pre-term neonates and infants up to 3 months of age with late-onset sepsis

Protocol number / Version	BPR-PIP-003 / 5.0
Compound	Ceftobiprole medocaril
Phase of development	Phase 3
IND number	64,407
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Project Physician	[redacted]
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Sponsor	Basilea Pharmaceutica International Ltd, Allschwil Hegenheimermattweg 167b 4123 Allschwil, Switzerland

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DOCUMENT APPROVAL

The original version of this document has been electronically signed by the representatives of Basilea Pharmaceutica International Ltd, Allschwil identified on page 1, in compliance with the requirements of (US) 21 CFR Part 11 and other applicable national regulations regarding electronic records and electronic signatures.

Name/Title	Date	Signature

PROTOCOL SYNOPSIS

TITLE:	A multicenter, open-label, single-arm, multiple-dose study to evaluate the safety, pharmacokinetics, and efficacy of ceftobiprole medocaril in term and pre-term neonates and infants up to 3 months of age with late-onset sepsis
PROTOCOL NUMBER / VERSION:	BPR-PIP-003 / 5.0
SPONSOR:	Basilea Pharmaceutica International Ltd, Allschwil
STUDY PHASE:	Phase 3
INDICATION:	Treatment of late-onset sepsis in term and pre-term neonates and infants up to 3 months of age
IND NUMBER:	64,407
EUDRACT NUMBER:	2022-001837-35
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OBJECTIVES

Primary objectives

To characterise the safety profile of ceftobiprole medocaril in term and pre-term neonates and infants up to 3 months of age with late-onset sepsis (LOS).[1]

Secondary objectives

To assess in term and pre-term neonates and infants up to 3 months of age with LOS treated with ceftobiprole medocaril:

- Pharmacokinetics (PK) of ceftobiprole
- Clinical response
- All-cause mortality
- Microbiological response

STUDY OVERVIEW

Study design

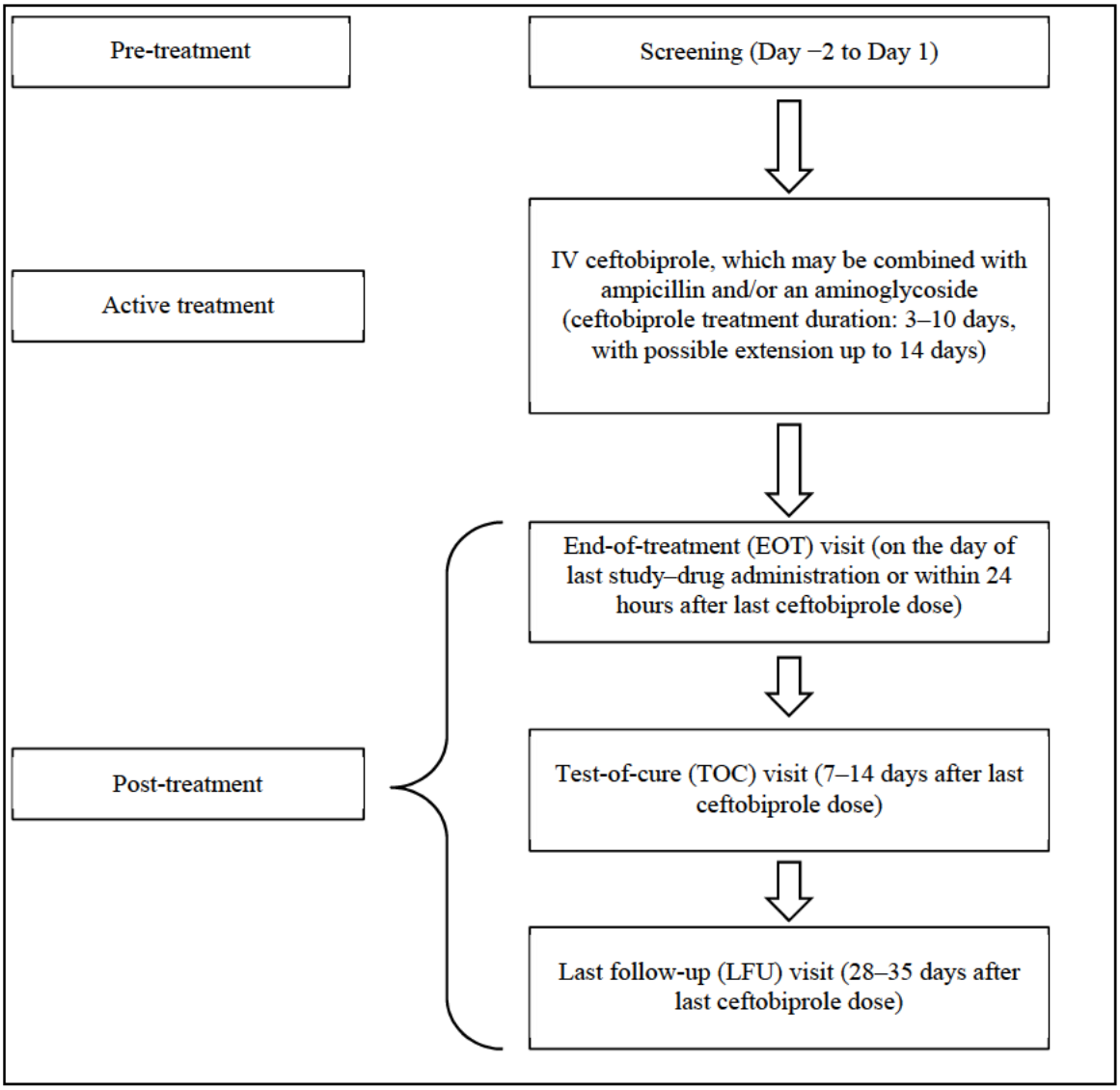
This is a multicenter, open-label, single-arm, multiple-dose study of intravenous (IV) ceftobiprole medocaril in term and pre-term neonates and infants up to 3 months of age with LOS. Ceftobiprole may be combined with ampicillin and/or an aminoglycoside based on the Investigator's judgement, local standard of care, and/or isolated or presumed pathogens.

[1] Ceftobiprole medocaril is the water-soluble prodrug of the active moiety ceftobiprole. Unless referring specifically to the prodrug, the term 'ceftobiprole' is used throughout the remainder of this protocol, and all doses are of ceftobiprole equivalents.

A Data and Safety Monitoring Board (DSMB) will review data on a regular basis to assess the safety of all patients enrolled in the study.

An overview of the study design is provided in Figure 1.

Figure 1 Overview of study design



EOT=end-of-treatment; IV=intravenous; LFU=last follow-up; TOC=test-of-cure.

PATIENT POPULATION

At least eight patients, at least two term (gestational age ≥ 37 weeks) and at least six pre-term (gestational age ≥ 24 to 36 weeks), with post-natal age ranging from ≥ 3 days to ≤ 3 months.

INVESTIGATIONAL PRODUCT(S)

Ceftobiprole medocaril powder for concentrate for solution for infusion.

NUMBER OF SITES/LOCATIONS

Approximately ten sites in Europe and USA, with additional sites and locations possible.

DOSE / ROUTE / REGIMEN

Ceftobiprole medocaril: 7.5 mg/kg every 12 hours to 15 mg/kg every 8 hours, (depending on age and weight) administered IV as a 2-hour infusion, with dose adjusted according to gestational and post-natal ages. Neonates and infants with a body weight < 4 kg will receive a maximum of 10 mg/kg/dose. The duration of treatment with ceftobiprole is 3–10 days, but may be extended to 14 days if considered clinically necessary by the Investigator.

Ampicillin and/or an aminoglycoside (gentamicin, tobramycin, or amikacin), if applicable: dosage and administration according to manufacturer's instructions and/or local standard of care. The treatment duration of ampicillin and/or the aminoglycoside, if added, is at the discretion of the Investigator.

KEY INCLUSION CRITERIA

(The full list of inclusion criteria is provided in Section 4.2 of the protocol.)

- Informed consent from parent(s) or other legally-acceptable representative (LAR) to participate in the study
- Male or female, with a gestational age of ≥ 24 weeks and a post-natal age ranging from ≥ 3 days to ≤ 3 months
- Diagnosis of documented or presumed bacterial LOS requiring administration of systemic antibiotic treatment
- Sufficient vascular access to receive study drug and to allow blood sampling at a site separate from the study drug infusion line

KEY EXCLUSION CRITERIA

(The full list of exclusion criteria is provided in Section 4.3 of the protocol.)

- Refractory septic shock not responding to 60 minutes of vasopressor treatment within 48 hours before enrollment
- Proven ventilator-associated pneumonia
- Proven central nervous system infection (e.g., meningitis, brain abscess)
- Proven osteomyelitis, infective endocarditis, or necrotising enterocolitis
- 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, OR urinary output < 0.5 mL/kg/h (measured over at least 8 hours), OR requirement for dialysis
- Progressively fatal underlying disease, or life expectancy < 30 days
- Use of systemic antibacterial therapy for longer than 72 hours within 7 days before start of study medication

- Participation in another clinical study with an investigational product within 30 days of enrollment in the current study

MAIN STUDY ENDPOINTS

Primary endpoint

- Safety and tolerability (Safety population):
  - Adverse events (AEs), serious AEs, deaths, and discontinuations due to AEs during treatment with ceftobiprole and at the end-of-treatment (EOT), test-of-cure (TOC), and last follow-up (LFU) visits
  - Clinical laboratory tests, vital signs, and physical examination findings

Secondary endpoints

- Pharmacokinetics (PK population):
  - Plasma levels of ceftobiprole, ceftobiprole medocaril, and open-ring metabolite
- Efficacy:
  - Clinical cure rate at the EOT and TOC visits (ITT and CE populations)
  - All-cause mortality through Day 28 (ITT population)
  - Microbiological eradication or presumed eradication rate at the EOT and TOC visits (mITT and ME populations)
  - Improved signs and symptoms of LOS at the Day 3, EOT, and TOC visits (ITT and CE populations)

STATISTICAL ANALYSIS

Key analysis populations

Intent-to-treat (ITT) population / Safety population

All patients enrolled in the study who received at least one dose of ceftobiprole.

Clinically Evaluable (CE) population

Patients in the ITT population who received at least 48 hours of study drug (i.e., four or six infusions of ceftobiprole as applicable) and had a completed overall clinical outcome assessment at the TOC visit, no major protocol deviations, and no concomitant systemic non-study antibiotic therapy.

Microbiological Intent-to-treat (mITT) population

All patients in the ITT population with a valid pathogen identified at baseline.

Microbiologically Evaluable (ME) population

All patients in the CE analysis population with a valid pathogen identified at baseline and a microbiological outcome assessment at the TOC visit.

Pharmacokinetics (PK) population

All patients who received at least one dose of ceftobiprole and had at least one sample of plasma concentration measurement obtained by the appropriate methodology.

Analyses

There will be no formal hypothesis testing. Descriptive statistics will be applied to the primary and secondary endpoints as follows: number, mean, standard deviation, median, minimum, and maximum will be provided for continuous variables, and frequency distributions (counts and

percentages) will be shown for categorical variables. All variables will be summarised overall and by gestational and post-natal ages as appropriate. Variables may be compared to baseline where applicable. Listings of individual patients' data will also be produced.

ASSESSMENTS

Safety/tolerability

Safety will be assessed through summaries of AEs, clinical laboratory tests, vital signs, and physical examination findings. All safety analyses will be based on the safety population.

Pharmacokinetics

Plasma concentrations of ceftobiprole, ceftobiprole medocaril, and open-ring metabolite. Descriptive analyses of these concentrations will be summarised by timepoint for term and pre-term neonates with post-natal age up to 3 months.

Clinical effect

The following efficacy assessments will be analysed using descriptive statistics:

- Clinical and microbiological outcome assessments at the EOT and TOC visits (Section 5.6)
- All-cause mortality through Day 28
- Signs and symptoms of LOS at the Day 3, EOT, and TOC visits (Section 5.6)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

% *f*T > MIC	Percentage of the dosing interval that free-drug concentrations are above the minimum inhibitory concentration
ABSSSI	Acute bacterial skin and skin structure infection
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CABP	Community-acquired bacterial pneumonia
CE	Clinically Evaluable
CI	Confidence Interval
C_{max}	Maximum concentration
CoNS	Coagulase-negative staphylococci
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End-of-treatment
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HABP	Hospital-acquired bacterial pneumonia
IB	Investigator's Brochure
ISF	Investigator Site File
ITT	Intent-to-treat
IV	Intravenous
LAR	Legally-acceptable representative
LFU	Last follow-up
LOS	Late-onset sepsis
ME	Microbiologically Evaluable
MIC	Minimum inhibitory concentration
mITT	Microbiological Intent-to-treat
MRSA	Methicillin-resistant *Staphylococcus aureus*

NOAEL	No-observed-adverse-effect level
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
q12h	Every 12 hours
q8h	Every 8 hours
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
T > MIC	Time above the minimum inhibitory concentration
TOC	Test-of-cure

1 INTRODUCTION

1.1 Disease characteristics and study drug

1.1.1 Disease characteristics

The incidence of neonatal sepsis is estimated at 2,824 cases per 100,000 live births (95% CI 1,892–4,194) and is inversely related to birth weight and gestational age, with a higher burden in low- and middle-income countries and a mortality ranging from 10.3% to 28.6% (Fleischmann 2021). Neonatal sepsis may be categorised as early onset (day of life 0–3) or late onset (day of life 4 or later) (Dong 2015). Early-onset sepsis is associated with acquisition of infection from the mother, mainly ascending from the cervix, or less commonly via hematogenous or transplacental spread. Late-onset sepsis (LOS) is attributed to organisms acquired from the environment, including coagulase-negative staphylococci (CoNS), *Staphylococcus aureus*, Enterobacterales, and *Pseudomonas* species (Dong 2015, Shane 2017). Empirical antibiotic treatment of LOS is typically guided by the antimicrobial resistance patterns of bacterial isolates commonly detected in the neonatal intensive care unit or in community settings. Given the increasing resistance among pathogens, alternative antibiotic treatments are needed.

1.1.2 Study drug

Ceftobiprole medocaril[2] is the water-soluble prodrug of ceftobiprole, an advanced-generation intravenous (IV) cephalosporin with bactericidal activity against a broad spectrum of Gram-positive (including CoNS and methicillin-resistant *S. aureus* [MRSA]) and Gram-negative (including Enterobacterales and *P. aeruginosa*) pathogens.

Ceftobiprole medocaril is approved for the treatment in adults of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in many European and non-European countries. It is currently under investigation to support a New Drug Application in the United States for the treatment in adults of acute bacterial skin and skin structure infections (ABSSSIs) and *S. aureus* bacteremia, including right-sided infective endocarditis.

In the context of the agreed European Paediatric Investigation Plan, three pediatric clinical studies were completed including a study to evaluate the single-dose safety and pharmacokinetics (PK) of ceftobiprole in neonates and infants up to 3 months of age. The purpose of the current study is to evaluate the safety, PK and efficacy of ceftobiprole, which may be combined with ampicillin and/or an aminoglycoside, in neonates and infants up to 3 months with LOS.

[2] Unless referring specifically to the prodrug, the term ‘ceftobiprole’ is used throughout the remainder of this protocol, and all doses are of ceftobiprole equivalents

1.2 Nonclinical studies with ceftobiprole

A comprehensive summary of nonclinical studies is provided in the Investigator's Brochure (IB).

1.2.1 Nonclinical pharmacodynamics and activity of ceftobiprole

Dose fractionation studies showed that the time above the minimum inhibitory concentration (T > MIC) is the pharmacokinetic-pharmacodynamic (PK-PD) index that correlated best with ceftobiprole activity, which is consistent with the beta-lactam class of antibiotics. In a neutropenic mouse thigh infection model, the %*f*T > MIC values required for the bacteriostatic doses were 14 to 28% for *S. aureus* (including MRSA) and *Streptococcus pneumoniae*, and 36 to 47% for Enterobacterales and *P. aeruginosa* (Craig 2008). The mean %*f*T > MIC for the 2-log kill dose for the strains of *S. pneumoniae* and *S. aureus* was 26% and 29%, respectively, while for the strains of Enterobacterales it was 65%. Ceftobiprole showed activities in the lung model similar to those in the thigh model.

The probability of target attainment was estimated by Monte Carlo simulation based on data from 150 adult subjects enrolled in Phase 1 and 2 studies analysed by using population PK modelling (Lodise 2007). For ceftobiprole 500 mg q8h administered as a 2-hour IV infusion, the probabilities of achieving 40% and 60% *f*T > MIC exceeded 90% for MICs < 4 and < 2 µg/mL, respectively. The probability of achieving a nearly maximal bactericidal effect (50% *f*T > MIC) exceeded 90% for *S. aureus* (including MRSA). For Gram-negative pathogens, the probability of achieving a nearly maximal bactericidal effect (60% *f*T > MIC) exceeded 90% for non-AmpC-producing isolates. This dose regimen was selected for the Phase 3 studies in adults with pneumonia and adults with ABSSSIs.

1.2.2 Nonclinical pharmacokinetics

In animal PK, toxicological, and infection model studies, IV ceftobiprole medocaril was rapidly hydrolyzed in plasma to the active moiety ceftobiprole by multiple enzymes, including plasma esterases, and also non-enzymatically. The volume of distribution of ceftobiprole was restricted to the extracellular compartment, and its elimination occurred predominantly by passive glomerular filtration of unchanged ceftobiprole. The beta-lactam open-ring was the main metabolic product.

In rats, excretion was almost complete within 4 days after IV administration of ceftobiprole medocaril. Penetration of ceftobiprole into lungs and brain in infected animals was demonstrated.

Based on cytochrome P450 inhibition data, the potential of ceftobiprole to exhibit clinically relevant drug-drug interactions is small. Protein binding of ceftobiprole in plasma of rats, rabbits, marmosets, cynomolgus monkeys, and dogs was low (approximately 10% to 45%) and concentration-independent. Plasma protein binding in humans was also low (approximately 16%) and concentration-independent.

Toxicokinetic monitoring during toxicity studies in rats, rabbits, marmosets, cynomolgus monkeys, and dogs demonstrated high and approximately dose-proportional exposures to

ceftobiprole in all species, exceeding the expected human therapeutic exposure at the no-observed-adverse-effect level (NOAEL). There were no relevant indications of accumulation, differences related to sex, or time-dependent PK.

In neonates and juveniles male and female rats administered daily from Day 1 post-partum until Day 49, which covers the human age range from neonates up to teenagers, dose-proportional exposure of the pups and decreased half-life and exposure to ceftobiprole with increasing age was demonstrated, as a consequence of increased renal clearance. There were no gender-differences. This study provides a safety margin of 2 to 6 for pediatric patients (neonates up to < 18 years) with the optimized dosing regimens.

1.2.3 Nonclinical toxicology

The toxicological profile of ceftobiprole was characterised in an extensive repeated-dose toxicity program that included systemic toxicity studies up to 13 weeks in rats, dogs and primates; reproductive toxicity; genotoxicity; local tolerability; and special studies to address the antigenic, phototoxic and nephrotoxic potential. In addition, juvenile toxicity was assessed in rats.

In rats, the primary targets of toxicity were the kidneys and the infusion site. Signs of vascular irritation at the IV infusion site were likely related to the large size of the catheter relative to that of the venous lumen. Vascular irritation by the test article was largely confined to the region of the vein damaged by the catheter, with little or no effect distal to the infusion site where the vein was exposed to the test article but not to the catheter. Toxicity to the kidneys was observed at doses ≥ 250 mg/kg, and was associated with the precipitation of drug-like material in the distal part of the nephron.

In dogs, reddening of the skin and mucous membranes was attributed to histamine release. No other relevant findings were observed.

In marmosets, thromboembolic effects secondary to infusion site reactions were observed, including thrombus formation at the catheter tip. Signs of vascular irritation at the IV infusion site were consistent with respective effects noted in rats, and were likely related to technical challenges inherent to chronic IV dosing in small animals. Findings in the kidneys were reversible and not associated with microscopic lesions. There were no indications of kidney toxicity related to precipitation as seen in rats.

Ceftobiprole medocaril was neither teratogenic nor embryotoxic in rats or cynomolgus monkeys, and had no effect on fertility and early embryonic development in rats. In a pre- and post-natal development study in rats, slight maternal toxicity was seen at high doses, but there were no direct effects on pups.

No mutagenic potential was seen in the Ames test or in the Chinese hamster ovarian assay.

Ceftobiprole medocaril exhibited low irritancy potential in rabbit local tolerance studies. No phototoxic potential was seen, and no hemolysis or precipitation was observed at concentrations ≤ 1.25%.

The toxicity of ceftobiprole medocaril in neonatal and juvenile rats was investigated in a study with 7-week once daily subcutaneous administration starting on Day 1 post-partum.

At the highest dose of 250 mg/kg/day (187.5 mg/kg/day ceftobiprole), effects on clinical condition and reduced body weight prior to weaning were seen. Differences in crown to rump and bone measurements were considered related to the lower body weight. Gross pathological and histopathological changes at the injection site were noted, and microscopic changes in the kidneys were seen at the end of treatment. Based on these findings, the NOAEL in juvenile rats was 100 mg/kg/day (75 mg/kg/day ceftobiprole).

In summary, the nonclinical toxicology profile of ceftobiprole is consistent with that seen with antibiotics of the beta-lactam class, and the observations in juvenile animals were similar to those seen in adult animals.

1.3 Clinical studies with ceftobiprole

The ceftobiprole clinical development program includes 32 completed studies: 21 Phase 1 studies in adult subjects, two Phase 1 studies (CSI-1006 and BPR-PIP-001) in pediatric patients, two Phase 2 studies in adult patients, five Phase 3 studies in adult patients, and one Phase 3 study (BPR-PIP-002) in pediatric patients.

One Phase 3 study (BPR-CS-009) in adult patients with *S. aureus* bacteremia is currently ongoing (Hamed 2020).

1.3.1 Completed Phase 3 clinical studies in adult patients

Table 1 gives an overview of key completed Phase 3 clinical studies in adult patients.

Table 1 Key completed Phase 3 clinical studies in adult patients

Study number / NCT number (Reference)	Study title	Number of patients	Study start Study end
BAP248/307 / NCT00210964 (Awad 2014)	A Phase 3, randomized, double-blind study of ceftobiprole medocaril versus linezolid plus ceftazidime in the treatment of nosocomial pneumonia	N=781 Ceftobiprole (n=391) Comparator (n=390)	06 Apr 2005 22 May 2007
CAP-3001 / NCT00326287 (Nicholson 2012)	Randomized, double-blind, multicenter study of ceftobiprole medocaril versus ceftriaxone with/without linezolid in treatment of subjects hospitalised with community-acquired pneumonia	N=638 Ceftobiprole (n=314) Comparator (n=324)	05 Jun 2006 19 Jul 2007
BPR-CS-008 / NCT03137173 (Overcash 2021)	A randomized, double-blind, multicenter study to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections	N=679 Ceftobiprole (n=335) Comparator (n=344)	19 Feb 2018 22 Apr 2019

In studies BAP248/307, CAP-3001, and BPR-CS-008, ceftobiprole was administered as a 2-hour 500 mg IV infusion every 8 hours.

In all completed Phase 3 studies in adult patients, the non-inferiority of ceftobiprole to comparator antibiotics was demonstrated within the pre-specified non-inferiority margin for the primary efficacy endpoint in each study.

Safety findings in the ceftobiprole clinical development program are consistent with the cephalosporin class effects and the underlying disease. Overall, treatment with ceftobiprole is well tolerated, with a manageable AE profile.

1.3.2 Completed studies in pediatric patients

Table 2 outlines completed clinical studies in pediatric patients.

Table 2 Completed clinical studies in pediatric patients

Study number / NCT number (Reference)	Study title	Phase	Number of patients	Study start Study end
CSI-1006 / NCT01026636 (Rubino 2021a)	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	1	N=64	08 Nov 2007 02 Apr 2010
BPR-PIP-001 / NCT03439124 (Rubino 2021b)	An open-label study to evaluate the single-dose pharmacokinetics and safety of ceftobiprole in neonate and infant patients aged up to 3 months undergoing treatment with systemic antibiotics	1	N=15	22 Nov 2016 07 Jul 2020
BPR-PIP-002 / NCT02527681 (Bosheva 2021)	A multicenter, randomized, Investigator-blind, active-controlled study to evaluate the safety, tolerability, pharmacokinetics and efficacy of ceftobiprole versus intravenous standard-of-care cephalosporin treatment with or without vancomycin in pediatric patients aged from 3 months to less than 18 years with hospital-acquired pneumonia or community-acquired pneumonia requiring hospitalisation	3	N=138 Ceftobiprole (n=94) Comparator (n=44)	27 Nov 2017 16 Mar 2020

1.3.2.1 Study CSI-1006

The primary objective of study CSI-1006 was to characterise the PK of ceftobiprole when administered as a 2-hour single-dose infusion in pediatric patients aged ≥ 3 months to < 18 years, who required therapeutic or prophylactic therapy with systemic antibiotics. The secondary objective was to evaluate the safety and tolerability of ceftobiprole in this study population.

This was a multicenter, open-label, single-dose, Phase 1 study that enrolled 64 pediatric patients in the following four age groups with documented or presumed, or at risk for, bacterial infections, and receiving systemic antibiotic therapy:

- 3 months to < 2 years (18 patients, 15 mg/kg)
- 2 years to < 6 years (15 patients, 15 mg/kg)
- 6 years to < 12 years (15 patients, 10 mg/kg)
- 12 years to < 18 years (16 patients, 7 mg/kg)

1.3.2.1.1 Pharmacokinetic results

Of the 62 patients who completed the study, 61 were included in the descriptive statistics of the ceftobiprole plasma concentrations, and 55 were included in the estimation of the plasma PK and exploratory PD parameters.

Overall, at the doses administered to patients aged < 12 years (15 mg/kg for patients aged < 6 years and 10 mg/kg for patients aged 6 years to < 12 years), the single-dose PK were generally within the range of what was previously observed in healthy adult subjects after a single ceftobiprole 500 mg dose. At the dose administered to patients aged 12 years to < 18 years (7 mg/kg, up to a maximum of 500 mg), the systemic exposure was substantially lower than that achieved in adults after a single ceftobiprole 500 mg dose.

1.3.2.1.2 Safety results

The safety assessments in this pediatric study showed that single-dose administration of ceftobiprole was safe and well tolerated by patients aged ≥ 3 months to < 18 years. No new or unexpected safety signals associated with ceftobiprole were detected.

1.3.2.2 Study BPR-PIP-001

The primary objective of study BPR-PIP-001 was to characterise the PK of ceftobiprole when administered as a 4-hour single-dose (7.5 mg/kg) infusion in neonates and infants aged ≤ 3 months. The secondary objective was to evaluate the safety and tolerability of ceftobiprole in this study population.

This was a multicenter, open-label, single-dose, Phase 1 study that planned to enroll 45 patients who had documented, or were presumed to be at risk of, bacterial infections, and who were already receiving systemic antibiotic therapy. This study enrolled 15 term neonates (gestational age ≥ 37 weeks).

1.3.2.2.1 Pharmacokinetic results

While all 15 patients enrolled in the study had measurable plasma concentrations, two patients had insufficient PK data for the non-compartmental analysis, and were therefore excluded from the PK analysis population.

Overall, exposure to the active moiety ceftobiprole was substantially higher than that for the prodrug ceftobiprole medocaril and the open-ring metabolite. The median maximum plasma concentration (C_{max}) was highest for ceftobiprole (11.2 µg/mL) compared to ceftobiprole medocaril (0.107 µg/mL) and the open-ring metabolite (0.644 µg/mL).

Ceftobiprole time to maximum concentration was reached at the end of infusion (i.e., at 4 hours) in all patients.

1.3.2.2.2 Safety results

The safety assessments in this pediatric study showed that single-dose administration of ceftobiprole at 7.5 mg/kg was safe and well tolerated by the neonate and infant population aged ≤ 3 months. No new or unexpected safety signals associated with ceftobiprole were detected.

1.3.2.3 Study BPR-PIP-002

The primary objective of study BPR-PIP-002 was to evaluate the safety profile of ceftobiprole in pediatric patients aged 3 months to < 18 years with hospital-acquired bacterial pneumonia (HABP) or community-acquired bacterial pneumonia (CABP) requiring hospitalisation and IV antibiotic therapy.

The secondary objectives were to characterise the PK of ceftobiprole and to evaluate the efficacy of ceftobiprole versus IV standard-of-care cephalosporin treatment (± vancomycin) in this patient population.

This was a multicenter, randomized (2:1), Investigator-blind, active-controlled study that enrolled 138 patients (94 in the ceftobiprole group and 44 in the comparator group). Patients randomized to ceftobiprole received IV infusions every 8 hours (q8h) at age–adjusted doses and infusion durations as follows:

- 3 months to < 2 years (12 patients, 20 mg/kg as 4-hour infusions)
- 2 years to < 6 years (37 patients, 20 mg/kg as 2-hour infusions)
- 6 years to < 12 years (27 patients, 15 mg/kg as 2-hour infusions)
- 12 years to < 18 years (18 patients, 10 mg/kg as 2-hour infusions)

1.3.2.3.1 Pharmacokinetic results

The PK population comprised 33 patients who received at least one dose of ceftobiprole and had at least one ceftobiprole plasma concentration measurement obtained. Of these, plasma concentration-time data were available for 29 patients. Exposure to ceftobiprole was substantially higher than that for the prodrug ceftobiprole medocaril and the open-ring metabolite. Ceftobiprole peaked at the end of infusion (4 hours for patients < 2 years and 2 hours for all other age groups).

In general, patients under 6 years of age (i.e., those who received ceftobiprole 20 mg/kg q8h) had higher ceftobiprole exposure and slightly longer half-life compared to patients aged 6 years or older. Mean C_{max} and area under the plasma concentration-time curve time zero to tau estimates were ~40% greater and half-life was ~16% longer in patients aged under 6 years compared to those 6 years or older (C_{max}: 33.3 versus 23.7 µg/mL; AUC_{tau}: 108 versus 77.6 h.µg/mL, respectively).

1.3.2.3.2 Safety results

The safety and tolerability of ceftobiprole in this study were consistent with the established safety profile for ceftobiprole in adults and with those of the cephalosporin class of

antibiotics. No new or unexpected safety signals associated with ceftobiprole were detected.

1.3.2.3.3 Efficacy results

Although the study was not powered to compare efficacy, this was the only pediatric study to-date that included efficacy objectives. The early clinical response rate at Day 4 was slightly higher in the ceftobiprole group than in the comparator group for both the intent-to-treat (ITT) and Clinically Evaluable (CE) populations, and at the test-of-cure (TOC) visit, the clinical cure rate was above 90% in both treatment groups, although lower in the ceftobiprole group than in the comparator group for both populations.

1.3.3 Benefit-risk assessment

Data from the clinical studies show that ceftobiprole can be safely administered to adult and pediatric (neonates to < 18 years of age) patients. Completed Phase 3 studies demonstrated the safety and efficacy of ceftobiprole in the adult population for various indications (HABP, CABP, and ABSSSI), and in the pediatric population the safety and efficacy in patients with bacterial pneumonia were similar to those observed in adult patients. One Phase 3 study is currently ongoing to evaluate the safety and efficacy of ceftobiprole for the treatment of *S. aureus* bacteremia in adult patients.

The potential benefit to patients participating in this study is receiving antibiotic therapy for their infection, and the potential benefit of this study in general is the identification of a new addition to the available antibiotic therapy that is safe and effective for the treatment of LOS. It is possible that ceftobiprole will not prove to be a sufficiently effective treatment for LOS. This risk is mitigated by the optional addition of ampicillin and/or an aminoglycoside, by close monitoring of study patients, and by management with appropriate therapies as determined by the Investigator. The risk considerations for this study encompass the known and potential risks for ceftobiprole, as well as those risks associated with other treatments that may be administered (i.e., ampicillin and/or an aminoglycoside) as described in their respective prescribing information.

1.4 Study rationale

This study is part of a pediatric clinical development program to evaluate the use of ceftobiprole in patients < 18 years of age. Three completed pediatric studies, two Phase 1 and one Phase 3, are described in Section 1.3.2. Study BPR-PIP-001 assessed the PK and safety of single-dose ceftobiprole in term neonates and infants aged ≤ 3 months.

LOS is a major cause of morbidity and mortality among neonates and young infants. Pathogens responsible for LOS include CoNS, *S. aureus*, Enterobacterales, and *P. aeruginosa*. Ceftobiprole has a broad-spectrum bactericidal activity against most of these organisms, and was well tolerated in adult and pediatric clinical studies with a safety profile consistent with that of available cephalosporins. Therefore, ceftobiprole has the potential to become a therapeutic option in the treatment of LOS.

The purpose of this study is to assess the safety, tolerability, PK, and clinical effect of ceftobiprole, possibly combined with ampicillin and/or an aminoglycoside, in neonates and young infants up to 3 months of age with LOS.

1.4.1 Summary of study design

This is a multicenter, open-label, single-arm, multiple-dose study of IV ceftobiprole in term and pre-term neonates and infants up to 3 months of age with LOS. Ceftobiprole may be combined with ampicillin and/or an aminoglycoside based on the Investigator's judgement, local standard of care, and/or isolated or presumed pathogens. At least eight patients, at least two term (gestational age ≥ 37 weeks) and at least six pre-term (gestational age ≥ 24 to 36 weeks), with post-natal age ranging from ≥ 3 days to ≤ 3 months will be enrolled.

The DSMB will review data on a regular basis to assess the safety of all patients enrolled in this study (see Section 3.4).

1.4.2 Study design rationale

A single-arm study design is based on practical considerations, mainly the feasibility of recruitment and study evaluation of pre-term and term neonates and young infants with LOS. As the incidence of LOS is inversely proportional to gestational age (i.e., almost double in pre-term neonates ≤ 32 weeks as compared to term neonates [Dong 2015]), twice as many pre-term neonates than term neonates will be enrolled.

Immediate administration of empiric antibiotic therapy with broad-spectrum bactericidal activity is critical in neonates and young infants with LOS, in order to prevent morbidity and decrease mortality. The optional combination with ceftobiprole of ampicillin and/or an aminoglycoside allows for maximal coverage of Gram-positive and Gram-negative pathogens of LOS, particularly during initial empiric treatment, and in accordance with local pathogen epidemiology and local standard of care.

1.4.3 Dose rationale

A three-compartment pediatric population PK model with linear elimination, clearance dependent on glomerular filtration, and other PK parameters scaled to body weight using a fitted coefficient consistent with allometric scaling principles, provided a robust fit to pooled data from studies CSI-1006, BPR-PIP-001, and BPR-PIP-002. Pre-defined model qualification procedures indicated that the final population PK model was expected to provide reliable estimates of ceftobiprole plasma exposure in the pediatric patients enrolled in these studies, and that the model was appropriate for the conduct of model-based simulations designed to identify appropriate ceftobiprole dosing regimens in pediatric patients (Rubino 2021a).

Model-based simulation analyses conducted using the final population PK model suggest that the following dosing regimens are predicted to result in consistent ceftobiprole exposure and adequate PK-PD target attainment for pathogens with a ceftobiprole MIC of 4 µg/mL (≥ 97.1% of the pediatric population with a %fT>MIC above 40%):

- ceftobiprole 10 mg/kg infused over 2 hours and administered q12h in neonates and infants aged < 3 months with a body weight < 4 kg
- ceftobiprole 15 mg/kg infused over 2 hours and administered q12h in neonates and infants aged < 3 months with a body weight ≥ 4 kg
- ceftobiprole 15 mg/kg infused over 2 hours and administered q8h in infants and children aged ≥ 3 months to < 12 years with a body weight < 33 kg
- ceftobiprole 10 mg/kg infused over 2 hours and administered q8h in adolescents aged ≥ 12 to < 18 years with a body weight < 50 kg
- ceftobiprole 500 mg infused over 2 hours and administered q8h in children with a body weight ≥ 33 kg and adolescents with a body weight ≥ 50 kg

Model-based simulations also indicated that the dose should be adjusted based on body weight or maximum allowable dose to avoid overly high exposures in the lightest infants (< 4 kg), children ≥ 33 kg, and adolescents ≥ 50 kg.

Extrapolation of the model to pre-term neonates and young infants was deemed appropriate given the dependence of ceftobiprole PK on glomerular filtration rate and body weight, which are both well described in this population. Glomerular filtration rate was assigned using a standard equation that assumed normal renal function, adjusted for age and body surface area using fat-free mass (Rhodin 2009). Body weight and height were assigned using a set of polynomial longitudinal growth equations, which define body weight and height over time based on gender, gestational age, and post-natal age (Troutman 2018).

Model-based simulation analyses to assist in the ceftobiprole dose selection for the treatment of LOS in pre-term and term neonates and young infants assessed several dose regimens before identification of an optimal regimen (Table 5). The optimal dose regimen, with dose adjustment according to gestational and post-natal ages, was predicted to result in a consistent ceftobiprole exposure and adequate PK-PD target attainment similar to those in adults and older pediatric patients. In general, the median predicted AUC0–24 values fall within the mean ± two standard deviations from the adult Phase 1 exposures from the multiple-ascending dose study. The 90% prediction intervals fall outside the range but remain acceptable. In contrast, ceftobiprole Cmax estimates were predicted to be lower than those observed in healthy adults, with the exception of the patients in the oldest gestational age group (≥ 37 weeks), which are similar to adults.

2 OBJECTIVES OF THE STUDY

2.1 Primary objective

To characterise the safety profile of ceftobiprole in term and pre-term neonates and infants up to 3 months of age with LOS.

2.2 Secondary objectives

To assess in term and pre-term neonates and infants up to 3 months of age with LOS treated with ceftobiprole:

- PK of ceftobiprole
- Clinical response
- All-cause mortality
- Microbiological response

3 STUDY DESIGN

This is a multicenter, open-label, single-arm, multiple-dose study of IV ceftobiprole in term and pre-term neonates and infants up to 3 months of age with LOS. At least eight patients, at least two term (gestational age ≥ 37 weeks) and at least six pre-term (gestational age ≥ 24 to 36 weeks), with post-natal age ranging from ≥ 3 days to ≤ 3 months will be enrolled at approximately ten sites in Europe and USA, with additional sites and locations possible.

Study therapy consists of IV ceftobiprole medocaril for 3–10 days, which may be extended to 14 days if considered clinically necessary by the Investigator. Ceftobiprole may be combined with ampicillin and/or an aminoglycoside based on the Investigator's judgement, local standard of care, and/or isolated or presumed pathogens. If added, the treatment duration of ampicillin and/or an aminoglycoside is at the discretion of the Investigator.

Each patient is expected to complete the study in approximately 5–7 weeks, including screening, an estimated treatment duration of 3–10 days with possible extension up to 14 days, end-of-treatment (EOT) visit, TOC visit 7–14 days after last ceftobiprole dose, and a last follow-up (LFU) visit 28–35 days after last ceftobiprole dose.

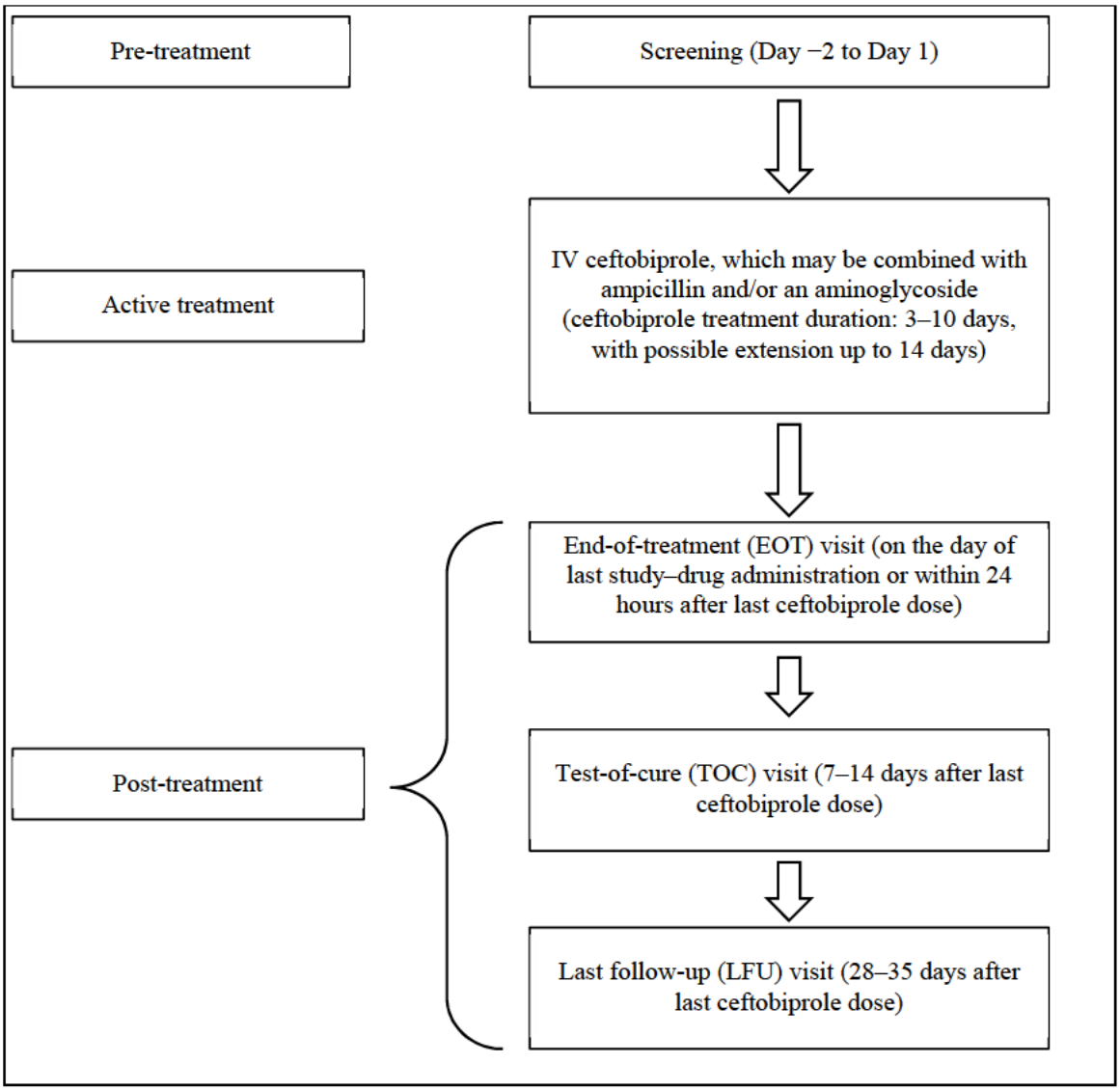
Safety assessments will be done throughout the study. Specimens for microbiological assessment will be obtained as clinically indicated in accordance with local standard of care. Blood samples for PK analysis will be collected on Day 3. Efficacy outcomes will be assessed at the EOT, TOC, and LFU visits.

The DSMB will review data on a regular basis to assess the safety of all patients enrolled in this study (see Section 3.4).

3.1 Overview of study design and dosing regimen

An overview of the study design is provided in Figure 1.

Figure 1 Overview of study design



EOT=end-of-treatment; IV=intravenous; LFU=last follow-up; TOC=test-of-cure.

Ceftobiprole medocaril powder for solution for infusion will be administered for 3–10 days (may be extended to 14 days if considered clinically necessary by the Investigator) as a 2-hour IV infusion according to the schedule in Table 5.

Ceftobiprole medocaril may be combined with IV ampicillin and/or an aminoglycoside (gentamicin, tobramycin or amikacin) based on the Investigator's judgement, local standard of care, and/or isolated or presumed pathogens.

3.2 Endpoints

3.2.1 Primary endpoint

The primary endpoint is safety and tolerability in the Safety population, as assessed by AEs, SAEs, deaths, and discontinuations due to AEs during treatment with ceftobiprole and at the EOT, TOC, and LFU visits, as well as clinical laboratory tests, vital signs, and physical examination findings.

3.2.2 Secondary endpoints

Pharmacokinetics

- Plasma levels of ceftobiprole, ceftobiprole medocaril, and the open-ring metabolite in the PK population

Efficacy

- Clinical cure rate at the EOT and TOC visits (ITT and CE populations)
- All-cause mortality through Day 28 (ITT population)
- Microbiological eradication or presumed eradication rate at the EOT and TOC visits (mITT and ME populations)
- Improved signs and symptoms of LOS at the Day 3, EOT, and TOC visits (ITT and CE populations)

3.3 Treatment plan

3.3.1 Dose modifications

The intended dose of IV ceftobiprole may not be modified. As patients with moderate or severe renal impairment will be excluded, no need for dose adjustment is expected. Study drug may be discontinued at any time at the Investigator's discretion (see Section 4.4). If a patient's estimated glomerular filtration rate (using the Schwartz formula or other applicable formula) decreases to less than two-thirds of normal for the applicable age group, or urinary output decreases to < 0.5 mL/kg/h (measured over at least 8 hours) during study drug treatment, ceftobiprole administration should be stopped and the patient should be switched to standard of care treatment. If continuation of ceftobiprole is considered necessary by the Investigator based on an individual medical benefit-risk assessment for a patient, then the implementation of real-time plasma level assessments of ceftobiprole is recommended.

If added, any dose modification for ampicillin and/or an aminoglycoside is at the discretion of the Investigator in accordance with local standard of care; aminoglycoside dose modification may be based on renal function or therapeutic drug monitoring.

3.3.2 Duration of treatment

The target treatment duration with IV ceftobiprole (administered as a 2-hour IV infusion according to the schedule in Table 5) is 3–10 days, which may be extended to 14 days if considered clinically necessary by the Investigator.

If added, the treatment duration of ampicillin and/or an aminoglycoside is at the discretion of the Investigator in accordance with local standard of care.

3.3.3 Missed-dose management

If one or more doses of IV ceftobiprole are missed, no additional doses are to be administered other than in accordance with the schedule provided in Table 5. In such cases, the Investigator may consider exclusion of the patient from the study after discussion with the medical monitor.

For ampicillin and/or an aminoglycoside, if added, management of missed doses is at the discretion of the Investigator in accordance with local standard of care.

3.3.4 Overdose

There is no available information on overdose with ceftobiprole in humans. The highest daily dose administered in Phase 1 clinical studies in adults was 3,000 mg (1,000 mg q8h). The range of doses administered in the Phase 1 pediatric study BPR-PIP-001 was 17.6 to 37.5 mg (5.8 to 7.5 mg/kg) in neonates and infants aged ≤ 3 months.

If an overdose occurs, it should be treated symptomatically. Symptomatic treatment may include treatment of gastrointestinal or central-nervous-system side effects (e.g., convulsions) which may be related to peak ceftobiprole plasma concentrations. Monitoring of plasma levels of ceftobiprole should therefore be considered. Ceftobiprole half-life is approximately 3.5 hours and plasma concentrations can be reduced by haemodialysis.

For ampicillin and/or an aminoglycoside, if added, see the respective local labels.

3.4 Data and Safety Monitoring Board

The composition, roles and responsibilities, and schedule of data review meeting of the DSMB are described in the DSMB Charter. The DSMB will review patient data on an ongoing basis to determine whether any safety concerns are observed, and whether the study should be allowed to continue.

3.5 Definition of the end of the study

The end of the study is defined as the completion of the last study-related contact with the last participant in the study.

4 STUDY POPULATION

4.1 Target population

Term (gestational age ≥ 37 weeks) and pre-term (gestational age ≥ 24 to 36 weeks) neonates and infants, with post-natal age ranging from ≥ 3 days to ≤ 3 months, meeting all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment in this study.

4.2 Inclusion criteria

For inclusion in the study, patients must meet **all** of the following criteria:

1. Informed consent from parent(s) or other legally-acceptable representative (LAR) to participate in the study
2. Male or female, with a gestational age of ≥ 24 weeks and a post-natal age ranging from ≥ 3 days to ≤ 3 months
3. Diagnosis of documented or presumed bacterial LOS requiring administration of IV antibiotic treatment.

   Patients must present with at least two of the clinical criteria and at least one of the laboratory criteria listed below:

   Clinical criteria (at least two):

   a) Hypothermia (< 36.6 °C / 97.9 °F rectal; < 36.5 °C / 97.7 °F axillary; < 35.5 °C / 95.9 °F oral; < 35.8 °C / 96.4 °F tympanic) OR fever (> 38.0 °C / 100.4 °F rectal; > 37.5 °C / 99.5 °F axillary; > 37.5 °C / 99.5 °F oral; > 38.0 °C / 100.4 °F tympanic)

   b) Bradycardia (< 100 beats/minute awake; < 80 beats/minute asleep) OR tachycardia (> 205 beats/minute awake; > 160 beats/minute asleep)

   c) Urinary output 0.5–1 mL/kg/h OR hypotension OR signs of impaired peripheral perfusion, such as mottled skin, moist and cold skin, finger to forearm temperature gradient, or increased capillary refill time

   d) Petechial rash OR sclerema neonatorum

   e) New onset or worsening of apnea episodes OR tachypnea episodes OR increased oxygen requirements OR requirement for ventilatory support (excluding underlying ventilator-associated pneumonia; see exclusion criteria)

   f) Feeding intolerance OR poor sucking OR abdominal distension

   g) Irritability

   h) Lethargy

   i) Muscular hypotonia

Laboratory criteria (at least one):

a) White blood cell count ≤ 4.0 × 10^9/L OR ≥ 20.0 × 10^9/L
b) Immature to total neutrophil ratio > 0.2
c) Platelet count ≤ 100 × 10^9/L
d) C-reactive protein > 15 mg/L OR procalcitonin ≥ 2 ng/mL OR Interleukin-6 (IL-6) elevated according to local laboratory thresholds
e) Hyperglycemia OR hypoglycemia
f) Metabolic acidosis

4. Sufficient vascular access to receive study drug and to allow blood sampling at a site separate from the study drug infusion line

4.3 Exclusion criteria

Patients who meet **any** of the following criteria must be excluded from the study:

1. History of a previous clinically relevant hypersensitivity or serious adverse reaction to beta-lactam antibiotics, or to aminoglycosides if intended to be used in combination with ceftobiprole
2. Viral, fungal, or parasitic pathogen as the sole reason for infection, OR known resistance of the causative bacterial pathogens to ceftobiprole
3. Refractory septic shock not responding to 60 minutes of vasopressor treatment within 48 hours before enrollment
4. Proven ventilator-associated pneumonia
5. Proven central nervous system infection (e.g., meningitis, brain abscess)
6. Proven osteomyelitis, infective endocarditis, or necrotising enterocolitis
7. 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, OR urinary output < 0.5 mL/kg/h (measured over at least 8 hours), OR requirement for dialysis
8. Significant laboratory abnormalities, including:
   a) Hematocrit < 20%
   b) Absolute neutrophil count < 0.5 × 10^9/L
   c) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 × the age-specific upper limit of normal
9. Progressively fatal underlying disease, or life expectancy < 30 days
10. Documented history of convulsions

11. Severe immunodeficiency (congenital or acquired)
12. Use of systemic antibacterial therapy for longer than 72 hours within 7 days before start of study medication
13. Any condition including antepartum / peripartum factors or procedures, which would, in the opinion of the Investigator, make the patient or caregiver unsuitable for the study, putting the patient at risk or compromising the quality of the data
14. Participation in another clinical study with an investigational product within 30 days of enrollment in the current study

4.4 Patient withdrawal

Parents or LARs may voluntarily withdraw consent for the patient's participation in the study at any time for any reason. The Investigator may also withdraw a patient from the study for reasons which may include adverse reactions (including but not limited to allergic-type reactions, infusion site reactions, or clinically relevant changes in vital signs), apparent infant distress, or at the request of the parent or the LAR.

If patients are withdrawn, the date of withdrawal and the reason for withdrawal must be recorded in the electronic case report form (eCRF).

If a patient who has received at least one dose of study drug discontinues treatment at any time for reasons other than withdrawal of consent, every effort must be made to complete the EOT and LFU visits.

Reasons for discontinuation of study treatment must be recorded, and may include:

- Adverse event
- Abnormal laboratory value
- Abnormal test procedure result
- Intercurrent illness that prevents further administration of treatment
- Diagnosis of any of the following conditions after enrollment in the study: ventilator-associated pneumonia, meningitis, brain abscess, osteomyelitis, infective endocarditis, or necrotising enterocolitis
- Confirmation of reduced susceptibility to ceftobiprole of any pathogen isolated
- Death
- Withdrawal of consent
- Withdrawn from the study at the Investigator's discretion
- Protocol deviation/non-compliance
- Lost to follow-up
- Administrative reasons

The reasons for discontinuation of study treatment must be recorded in the eCRF.

For all patients who discontinue study treatment, AE monitoring must be continued up to and including the LFU visit. For patients who fail to return for the LFU visit, the

Investigator must make every effort to contact the parent(s) or LAR (by telephone or mail correspondence). The outcome of this contact must be documented by the Investigator and filed in the Investigator Site File (ISF).

4.5 Replacement of patients

Patients failing screening procedures are to be replaced.

Patients who for any reason discontinue participation in the study after enrollment but prior to receiving the first dose of study drug are to be replaced.

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

4.6 Study discontinuation

The Sponsor reserves the right to temporarily or permanently discontinue the study at any time. Reasons for study discontinuation may include, but are not limited to:

- Safety concerns (an identified risk or potential risk that could have an impact on the benefit-risk balance of the product or implications for public health).
- Poor enrollment.
- Non-compliance with the protocol, Good Clinical Practice (GCP) guidelines, or other regulatory requirements by the Investigator(s).
- Request to discontinue the study by a Health Authority.
- Enrollment to either study group (term or pre-term) will be discontinued after the minimum number of patients to the group is reached. Enrollment to the other group will continue until the minimum required number of patients is also reached.

The Sponsor will ensure that all Investigators and the appropriate Health Authorities are promptly informed if the study is suspended or terminated prematurely for safety reasons. In the event of such a termination, the Investigator will also promptly notify the IEC/IRB.

5 SCHEDULE OF ASSESSMENTS AND PROCEDURES

5.1 Summary of schedule of assessments

Table 3 presents a summary of the schedule of assessments to be performed from screening through the LFU visit.

Adverse events will be monitored on an ongoing basis and at each study visit, beginning on study Day 1. Adverse event monitoring must be continued up to the LFU visit (see Section 7.4).

Table 3 Schedule of assessments

Visit name	**Screening / Baseline**	**Active treatment (Days 1, 2, 3, 4–10, and, if applicable, 11–14)[1]**					**EOT[2]**	**TOC**	**LFU[3]**
Assessment window	**Day −2 to Day 1**	**Day 1**	**Day 2**	**Day 3**	**Days 4–10**	**Days 11–14, only if applicable**	**Within 24 h after last dose**	**7–14 days after last dose**	**28–35 days after last dose**
Written informed consent[4]	X								
Inclusion/exclusion criteria	X								
Medical history and demographics (including antepartum/peripartum period)	X								
Prior medications[5]	X								
Physical examination[6]	X	X[6]					X	X	
Length	X								
Weight[7]	X	X[7]	X	X	X	X	X	X	
Vital signs and pulse oximetry[8]	X	X[8]	X[8]	X[8]	X[8]	X[8]	X	X	
Signs and symptoms of LOS	X	X	X	X	X	X	X	X	
Hematology, blood chemistry, urinalysis[9]	X	X[9]					X	X[9]	
Anion gap, C-reactive protein, procalcitonin, IL-6 (optional)[10]	X[10]	X[10]							
Urine output[11]	X[11]	X[11]							
Imaging tests (optional)[12]	X[12]	X[12]							
Microbiological sampling[13]	X[13]	X[13]							
Overall clinical outcome assessment[14]							X	X	

Microbiological outcome assessment[15]							X	X	
Study drug administration[1]		X	X	X	X	X[1]			
Concomitant medications[16]		X	X	X	X	X	X	X	X
Concomitant medical procedures		X	X	X	X	X	X	X	X
Adverse event assessment[17]		X	X	X	X	X	X	X	X
PK blood sampling[18]				X					
Aminoglycoside monitoring, if applicable[19]		X[19]							
Survival status[20]									X
Relapse assessment									X

EOT=end of treatment; LFU=last follow-up; LOS=late-onset sepsis; PK=pharmacokinetics; TOC=test of cure.

1 The duration of treatment with ceftobiprole (i.e., study drug) is 3–10 days, but this may be extended to 14 days if considered clinically necessary by the Investigator if in accordance with local standard of care (see Section 3.3.2). The duration of treatment with ampicillin and/or an aminoglycoside antibiotic, if given in combination with ceftobiprole, is at the Investigator's judgment in accordance with local standard of care (i.e., may be terminated at any time if considered appropriate by the Investigator) and must be recorded.[16]
2 EOT assessment is to be performed on the day of last study drug administration, or as a separate visit within 24 hours of last study-drug administration.
3 The LFU visit may be performed by telephone contact if the patient has been discharged from the hospital, unless an examination is needed to evaluate relapse or abnormalities recorded during the TOC visit (see Section 5.2.5).
4 Written informed consent (or, in the event of an emergency, verbal informed consent followed by written consent as soon as the situation allows) must be obtained before any study-specific procedures or assessments take place (see Section 10.2).
5 Prior medications taken within 7 days before the first dose of study drug is to be recorded. For patients who are being breastfed, all medications taken by the lactating mother within 3 days before the first dose of study drug is to be recorded.
6 Complete physical examination is to be performed at Screening, the EOT visit, and the TOC visit. Complete or targeted physical examinations focusing on changes from baseline is to be performed during the active treatment period at the discretion of the Investigator as clinically indicated in accordance with local standard of care (see Section 5.5.2).
7 Body weight on Day 1, which is to be used for Day 1 dose calculation, should be obtained within 12 hours prior to the first dose of study drug. From Day 2 until the last day of study treatment, the dose should be calculated based on the patient's first body weight of the day (see Section 5.5.2).
8 Vital signs (including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) and pulse oximetry must be recorded within 30 minutes before the first study drug administration, and then three times daily during the active treatment period; if continuously monitored, the highest body temperature, respiratory rate, and pulse rate, and the lowest systolic and diastolic blood pressures and oxygen saturation obtained during an 8-hour period, are to be recorded. Vital signs and pulse oximetry must also be obtained at the EOT and the TOC visits (see Section 5.5.3).

9 Hematology, blood chemistry, and urinalysis are to be performed at baseline and at the EOT visit. At all other visits, these laboratory evaluations are to be performed only if clinically indicated based on the Investigator's judgment in accordance with local standard of care (for details, see Sections 5.2.2, 5.2.4, and 5.5.4).
10 Optional assessment of anion gap, C-reactive protein, procalcitonin, and IL-6 at any time from Screening until the end of active treatment, if considered clinically indicated by the Investigator in accordance with local standard of care.
11 If clinically indicated, measurement of urine output should be done over at least an 8-hour period. Use of a urinary catheter is based on the Investigator's judgment in accordance with local standard of care. Urinary catheters are not required for the purposes of this study (see Sections 5.2.1, 5.2.2).
12 Results of imaging tests (e.g., chest X-ray, ultrasound, CT scan, MRI) performed as part of the patient's standard clinical care within 72 hours before start of study treatment are to be recorded in the eCRF. From Day 1 up to and including the TOC visit, imaging tests are to be performed if clinically indicated based on the Investigator's judgment in accordance with local standard of care.
13 Screening/baseline and post-baseline blood specimens and any other specimens (e.g., urine, cerebrospinal fluid) for microbiological evaluation should be obtained as clinically indicated in accordance with local standard of care and as described in the Laboratory Manual.
14 At the EOT and TOC visits, the Investigator must rate the overall clinical outcome as 'clinical cure', 'clinical failure', or 'unevaluable'.
15 Microbiological outcome is to be assessed only in patients with valid pathogens identified at the Screening/Baseline visit. For details, see Section 5.6.3.
16 All medications taken after the recording of prior medications, and medications continued after enrollment in the study, should be recorded as concomitant therapy. For patients who are being breastfed, all concomitant medications taken by the lactating mother up to the LFU visit are to be recorded.
17 See Section 7.4.
18 PK blood sampling is to be done on treatment Day 3 as described in the Laboratory Manual: pre-dose before the first ceftobiprole infusion, at 2 hours (end of infusion), 4 hours, and 8 hours. PK samples should not be taken from the infusion lines. See Section 5.7.
19 In the event of combination treatment with an aminoglycoside, monitoring of aminoglycoside blood levels and monitoring for ototoxicity and/or nephrotoxicity should be performed according to recommendations in the local label and local standard of care.
20 Survival status is to be assessed.

5.2 Study visits

Parent(s) or a LAR must provide written informed consent before any study-specific assessments or procedures are performed (see Section 10.2 for details).

5.2.1 Screening visit / Baseline (Day −2 to Day 1)

The following assessments and procedures will be performed at the screening visit (Day −2 to Day 1; see Table 3):

- Medical history and demographics, including the antepartum/peripartum period (see Section 5.3.1)
- Review and recording of medications taken within 7 days before the first dose of study drug. For patients who are being breastfed, medications taken by the lactating mother within 3 days before the first dose of study drug will also be recorded.
- Physical examination (see Section 5.5.2)
- Length and body weight (see Section 5.5.2)
- Vital signs (including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) and pulse oximetry (see Section 5.5.3)
- Signs and symptoms of LOS (see Section 5.6.4)
- Local laboratory tests: results will be used for the assessment of inclusion/exclusion criteria and throughout the study (for details, see Sections 4.2, 4.3, and 5.5.4). Laboratory tests required as part of the screening process which have been performed within 48 hours prior to the first dose of study drug do not need to be repeated, regardless of whether they were performed before or after signing of the informed consent form (ICF).
- If clinically indicated, measurement of urine output (over at least an 8-hour period) in patients hospitalised ≥ 8 hours before study drug dosing. Use of a urinary catheter is based on the Investigator's judgement in accordance with local standard of care. Urinary catheters are not required for the purposes of this study.
- Recording of results of imaging studies (e.g., chest X-ray, ultrasound, CT scan, MRI) performed as part of the patient's standard of care within 72 hours before the first dose of study drug.
- Collection of blood and other specimens for microbiological evaluation as clinically indicated based on the Investigator's judgement in accordance with local standard of care (see Section 5.4)

The Investigator will review the results of the screening assessments and procedures, including results of laboratory tests, and all inclusion/exclusion criteria to ensure patient eligibility.

5.2.2 Active treatment visits

The following assessments and procedures will be performed during study treatment visits (Day 1 to Day 10 [or up to Day 14]; see Table 3):

- Study drug administration should be initiated as soon as possible after enrollment. Ceftobiprole medocaril will be reconstituted and diluted for IV administration and administered as described in the Pharmacy Manual and in Section 6.6. If applicable, ampicillin and/or an aminoglycoside will be prepared and administered according to the manufacturer's instructions and/or local standard of care. The dates and exact start and stop times of all ceftobiprole infusions, and if applicable, of all ampicillin and/or aminoglycoside infusions/injections must be recorded in the eCRF.
- Physical examination: complete or brief physical examinations focusing on changes from baseline during the active treatment period will be performed at the discretion of the Investigator as clinically indicated in accordance with local standard of care (see Section 5.5.2)
- Body weight (see Section 5.5.2): body weight on Day 1, which will be used for Day 1 dose calculation, should be obtained within 12 hours prior to the first dose of study drug. From Day 2 until the last day of study treatment, the dose should be calculated based on the patient's first body weight of the day.
- Vital signs (including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) and pulse oximetry must be recorded within 30 minutes before the first study drug administration, and then three times daily during the active treatment period. If continuously monitored, the highest body temperature, respiratory rate, and pulse rate, and the lowest systolic and diastolic blood pressures and oxygen saturation obtained during an 8-hour period, will be recorded (see Section 5.5.3).
- Signs and symptoms of LOS (see Section 5.6.4)
- Local laboratory tests will be performed only if clinically indicated based on the Investigator's judgement in accordance with local standard of care (see Section 5.5.4).
- If clinically indicated, measurement of urine output (over at least an 8-hour period). Use of a urinary catheter is based on the Investigator's judgement in accordance with local standard of care. Urinary catheters are not required for the purposes of this study.
- Imaging studies (e.g., chest X-ray, ultrasound, CT scan, MRI) will be performed if clinically indicated based on the Investigator's judgement in accordance with local standard of care.
- Collection of blood and other specimens for microbiological evaluation as clinically indicated based on the Investigator's judgement in accordance with local standard of care (see Section 5.4).
- Review and recording of concomitant medications, including ongoing prior medications, and concomitant medical procedures, including ongoing prior procedures.
- Adverse events must be monitored and recorded on an ongoing basis as outlined in Section 7.4.

- PK blood sampling on Day 3: blood samples for measurement of ceftobiprole, ceftobiprole medocaril, and open-ring metabolite concentrations will be collected pre-dose and at 2 hours (end of infusion), 4 hours, and 8 hours, as described in detail in the Laboratory Manual (see Section 5.4). PK samples should not be taken from the infusion lines.
- If applicable, determination of aminoglycoside blood levels and monitoring for ototoxicity and nephrotoxicity should be performed according to the recommendations provided in the local label and/or local standard of care.

5.2.3 End-of-treatment visit

The following assessments and procedures will be performed at the EOT visit (on the day of last study–drug administration or within 24 hours of the last dose of study drug; see Table 3):

- Physical examination (see Section 5.5.2)
- Body weight (see Section 5.5.2)
- Vital signs (including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) and pulse oximetry (see Section 5.5.3)
- Signs and symptoms of LOS (see Section 5.6.4)
- Local laboratory tests (see Section 5.5.4)
- Collection of blood and other specimens for microbiological evaluation as clinically indicated based on the Investigator's judgement in accordance with local standard of care (see Section 5.4)
- Imaging tests (e.g., chest X-ray, ultrasound, CT scan, MRI) will be performed if clinically indicated based on the Investigator's judgement in accordance with local standard of care.
- Overall clinical outcome assessment: clinical cure, clinical failure, or unevaluable (see Section 5.6.1)
- Microbiological outcome assessment: eradication, presumed eradication, persistence, presumed persistence, or unevaluable (see Section 5.6.3)
- Review and recording of changes in concomitant medications and concomitant procedures
- Adverse events must be monitored and recorded as outlined in Section 7.4.

5.2.4 Test-of-cure visit

The following assessments and procedures will be performed at the TOC visit (7−14 days after the last dose of study drug; see Table 3):

- Physical examination (see Section 5.5.2)
- Body weight (see Section 5.5.2)
- Vital signs (including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) and pulse oximetry (see Section 5.5.3)

- Signs and symptoms of LOS (see Section 5.6.5)
- Local laboratory tests will be performed only if clinically indicated based on the Investigator's judgement in accordance with local standard of care (see Section 5.5.4)
- Imaging tests (e.g., chest X-ray, ultrasound, CT scan, MRI) will be performed if clinically indicated based on the Investigator's judgement in accordance with local standard of care.
- Collection of blood and other specimens for microbiological evaluation as clinically indicated based on the Investigator's judgement in accordance with local standard of care (see Section 5.4).
- Overall clinical outcome assessment: clinical cure, clinical failure, or unevaluable (see Section 5.6.1)
- Microbiological outcome assessment: eradication, presumed eradication, persistence, presumed persistence, or unevaluable (see Section 5.6.3)
- Review and recording of changes in concomitant medications and concomitant procedures
- Adverse events must be monitored and recorded as outlined in Section 7.4.

5.2.5 Last follow-up visit

The following assessments and procedures will be performed at the LFU visit (28−35 days after the last dose of study drug; see Table 3). This visit can be done by telephone contact unless an examination is needed to evaluate relapse or abnormalities recorded during the TOC visit.

- Review and recording of changes in concomitant medications and concomitant procedures
- Adverse events must be monitored and recorded as outlined Section 7.4.
- Survival status
- Relapse assessment: Deterioration of the clinical condition compared to the TOC visit, microbiological recurrence, or the requirement for additional antimicrobial therapy for LOS

5.3 Medical history and concomitant medications

5.3.1 Medical history

A full medical history, including relevant abnormalities, surgeries, diseases, or disorders, must be obtained at Screening.

Medical history also includes any relevant worsening of a patient's condition which occurs after consent, but prior to the start of first study-drug administration (see Section 7.2.1).

5.3.2 Prohibited concomitant medications

- Systemic antibacterial therapy other than ampicillin and aminoglycosides

5.3.3 Permitted concomitant medications

- Ampicillin and/or an aminoglycoside based on the Investigator's judgement, local standard of care, and/or isolated or presumed pathogens
- Topical antibacterial medications
- Acetaminophen or paracetamol
- Nonsteroidal anti-inflammatory drugs and systemic steroids
- Non-antibacterial standard-of-care medications

5.4 Microbiology assessments

Microbiological evaluation and outcome assessment may be based on blood samples, urine, cerebrospinal fluid, or any other suitable specimen samples.

If clinically indicated and performed as part of the patient's regular medical care, blood is to be obtained for microbiological evaluation at the Screening visit/Baseline (if possible before any antibiotics are administered), or at any time through to LFU visit. Cultures should be repeated in accordance with standard of care if a positive result is obtained, until sterilization is confirmed. Gram stain, culture/PCR, and organism identification are to be performed at the local or regional laboratory, as applicable. All isolates, regardless of specimen source, are to be sent to the central microbiology laboratory for final organism identification and study-specific susceptibility testing.

See the Laboratory Manual for procedures regarding the collection, processing, storage, and shipment of pathogens. Rules for the assessment of the validity of pathogens are described in the Statistical Analysis Plan (SAP).

5.5 Safety assessments

The Investigator will evaluate safety by AE monitoring, clinical laboratory tests, vital signs, and physical examination (see schedule of assessments; Table 3).

Safety assessments must be performed at intervals indicated in the schedule of assessments (Table 3). More frequent assessments may be performed at the Investigator's discretion, if medically indicated.

Safety data will be reviewed by the Sponsor and by the DSMB (see Section 3.4).

5.5.1 Adverse event monitoring

See Section 7.4 for details regarding AE collection and management.

5.5.2 Physical examination

A complete physical examination will be performed at Screening and at the EOT and TOC visits in accordance with Table 3, and will include examination of general appearance, skin, head, neck, eyes, ears, nose, throat, cardiovascular system, thorax/lungs, abdomen, lymph nodes, extremities, and nervous system.

Complete or targeted physical examinations focusing on changes from baseline will be performed during the active treatment period at the discretion of the Investigator as clinically indicated in accordance with local standard of care.

Any clinically-significant physical change from baseline that occurs after first study-drug

administration must be reported as an AE (see Section 7.4).

A patient's length will be measured only during the Screening visit.

Body weight will be measured at Screening, daily during the active treatment period, and at the EOT and TOC visits. The weight obtained within 12 hours prior to the first dose of study drug will be used to calculate the dose on Day 1. From Day 2 until the last day of study treatment, the dose should be calculated based on the patient's first body weight of the day.

5.5.3 Vital signs and pulse oximetry

Vital signs (including body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) and pulse oximetry must be recorded during all visits from Screening up to and including the TOC visit (Table 3). During the active treatment period, vital signs must be recorded within 30 minutes before the first study drug administration, and then three times daily; if continuously monitored, the highest body temperature, respiratory rate, and pulse rate, and the lowest systolic and diastolic blood pressures and oxygen saturation obtained during an 8-hour period, will be recorded.

5.5.4 Laboratory parameters and PK sampling

The local laboratory tests include haematology, blood chemistry and urine analysis (dipstick) parameters as per the schedule of assessments (Table 3) and Table 4. Additional testing may be performed whenever clinically indicated at the discretion of the Investigator. All samples for a given study site must be analysed by the same local laboratory throughout the study, as designated by the Investigator. The results are to be printed, signed and dated by the Investigator or his/her designee.

In the event of unexplained abnormal laboratory test values, the tests must be repeated and followed up until return to the normal range, stabilisation, and/or until an adequate explanation of the abnormality has been determined. When a clear explanation is established this must be recorded in the eCRF.

Table 4 Local laboratory parameters

Mandatory at Screening and the EOT visit; optional at active treatment visits and the TOC visit:		
Haematology	**Blood chemistry**	**Urine analysis (dipstick)**
Haematocrit	ALT	Blood
Red blood cell count	AST	Glucose
White blood cell count	Bilirubin (total)	Ketones
Absolute and immature neutrophils	Creatinine	Leukocytes
Platelets	Sodium	Nitrite
	Potassium	pH
	Bicarbonate	Protein
Optional at Screening and active treatment visits:		
	Blood chemistry	
	Anion gap	
	C-reactive protein	
	Procalcitonin	
	IL-6	

EOT=end-of-treatment; ALT=alanine aminotransferase; AST=aspartate aminotransferase; TOC= test-of-cure.
Note: Optional blood tests may be performed at the discretion of the Investigator in accordance with local standard of care, taking into consideration the maximum allowable blood draw volumes.

See the Laboratory Manual for blood volumes to be drawn from each patient for the local laboratory tests and for PK sampling. The combined volume of blood samples taken for study purposes or as part of standard of care must not exceed the limit specified in the Laboratory Manual. Any deviations from this must be clinically justified.

5.5.5 Pregnancy testing

Not applicable.

5.6 Efficacy assessments

5.6.1 Overall clinical outcome

At the EOT and TOC visits, the Investigator must assess the overall clinical outcome as:

- ***Clinical cure***
  - Signs and symptoms of LOS improved or normalised to an extent that no further antibacterial therapy is required
- ***Clinical failure***
  - Discontinuation of study treatment and requirement for non-study antibacterial therapy because of:
    - Insufficient therapeutic effect associated with study treatment, including persistence or worsening of signs and symptoms of LOS
    - AE related to the study treatment
  - Death attributable to LOS

- ***Unevaluable***
  - Study data not available for evaluation of efficacy for any reason, including:
    - Lost to follow-up
    - Received < 48 hours of study treatment
    - Concomitant treatment with a systemic antibacterial administered for a reason other than LOS, which is active against the isolated LOS pathogen, or in the absence of microbiological evaluation, is active against common LOS pathogens
    - Diagnosis of any of the following conditions after enrollment in the study and discontinuation of study treatment: ventilator-associated pneumonia, meningitis, brain abscess, osteomyelitis, infective endocarditis, or necrotising enterocolitis
    - Death in which LOS is clearly non-contributory
    - Absence of clinical assessment for any reason

5.6.2 All-cause mortality

Vital status will be assessed at the LFU visit, whether performed in person or by telephone contact.

5.6.3 Microbiological outcome

The microbiological outcome categories at EOT and TOC are defined below. For a patient to have a favorable microbiological response, the outcome for each baseline pathogen must be eradicated or presumed eradicated. If the outcome for any pathogen is persistence or presumed persistence, the patient will be considered to have an unfavorable microbiological response.

Microbiological outcome is to be assessed at the EOT and TOC visits by the Investigator as follows

- ***Eradication***: Absence of baseline pathogen in follow-up cultures of source specimen
- ***Presumed eradication***: Absence of follow-up microbiological evaluation of source specimen, or unavailable microbiological results, for a patient with a valid baseline pathogen who was assessed as a clinical cure
- ***Persistence***: Continued presence of a baseline pathogen in follow-up cultures of any source specimen
- ***Presumed persistence***: Absence of follow-up microbiological evaluation of source specimen or unavailable microbiological results for a patient with a valid baseline pathogen and assessed as a clinical failure
- ***Unevaluable***: No valid pathogen identified at baseline, or no follow-up microbiological evaluation of source specimen obtained in a patient with clinical outcome assessed as unevaluable
- ***Relapse***: Baseline pathogen detected again in follow-up microbiological evaluation of any source specimen obtained between the TOC and LFU visits after documented eradication or presumed eradication at the TOC visit (note: this applies only to the microbiological outcome assessment at the LFU visit)

5.6.4 Relapse at LFU

At the LFU visit, the Investigator must assess relapse as follows:

- Deterioration of the patient's clinical condition compared to the TOC visit, microbiological recurrence, or the requirement for additional antimicrobial therapy for LOS

5.6.5 Signs and symptoms of LOS

The Investigator must rate the following signs and symptoms of LOS as:

- 'absent' or 'present' at baseline (pre-dose)
- 'absent', 'improved', 'unchanged' or 'worsened' compared to baseline, on every day of active study treatment, and at the EOT, TOC, and LFU visits

1. Fever (> 38.0 °C / 100.4 °F rectal; > 37.5 °C / 99.5 °F axillary; > 37.5 °C / 99.5 °F oral; > 38.0 °C / 100.4 °F tympanic)
2. Hypothermia (< 36.6 °C / 97.9 °F rectal; < 36.5 °C / 97.7 °F axillary; < 35.5 °C / 95.9 °F oral; < 35.8 °C / 96.4 °F tympanic)
3. Abnormal heart rate
   a. Bradycardia (< 100 beats/minute awake; < 80 beats/minute asleep)
   b. Tachycardia (> 205 beats/minute awake; > 160 beats/minute asleep)
4. Signs of impaired circulation
   a. Urine output 0.5–1 mL/kg/h (in patients with urinary catheters; note: urinary catheters are not required for the purposes of this study)
   b. Hypotension
   c. Signs of impaired peripheral perfusion, such as mottled skin, moist and cold skin, finger to forearm temperature gradient, or increased capillary refill time
5. Petechial rash OR sclerema neonatorum
6. Respiratory distress
   a. New onset or worsening of apnea episodes
   b. Tachypnea episodes
   c. Increased oxygen requirements
   d. Requirement for ventilatory support (note: proven ventilator-associated pneumonia is an exclusion criterion; see Section 4.3)
7. Gastrointestinal distress
   a. Feeding intolerance
   b. Poor sucking
   c. Abdominal distension
8. Irritability
9. Lethargy
10. Muscular hypotonia

5.7 Pharmacokinetic assessments

PK will be assessed by means of sparse blood sampling on Day 3: pre-dose and at 2 hours (end of infusion), 4 hours, and 8 hours, as described in detail in the Laboratory Manual. PK samples should not be taken from the infusion lines.

6 STUDY TREATMENT

6.1 Blinding

This is an open-label study.

6.2 Randomization

This is a single-arm study. At least two term (gestational age ≥ 37 weeks) and six pre-term (gestational age ≥ 24 to 36 weeks) neonates and infants, with post-natal age ranging from ≥ 3 days to ≤ 3 months will be enrolled, with no stratification.

6.3 Packaging and labelling

The study drug will be packed and labelled in accordance with local regulations and the Annex 13 Good Manufacturing Practice rules. Labels will include the identity of the Sponsor and Investigator, protocol number, drug identification, storage conditions, content of study drug, and expiry date. Information on drug shipment including temperature logger and acknowledgement of receipt form to be completed by the receiver will also be included.

6.4 Shipping and storage conditions

Vials of sterile lyophilised ceftobiprole medocaril containing the equivalent of 500 mg ceftobiprole will be shipped to the study sites, and the dry powder must be stored in a refrigerator (2−8 °C / 36−46 °F). All study drug must be kept under secure conditions, e.g., in the hospital pharmacy.

Further information on the shipping and storage conditions is provided in the Pharmacy Manual.

6.5 Preparation, presentation, and stability of study drug

Details on the presentation, preparation (including reconstitution and dilution steps), and stability of study drug are provided in the Pharmacy Manual.

6.6 Dosage and administration of study drug

Eligible patients will receive ceftobiprole as a 2-hour IV infusion according to the schedule in Table 5, with dose adjusted according to gestational and post-natal ages. Body weight on Day 1 should be obtained within 12 hours prior to the first dose of study drug. From Day 2 until the last day of study treatment, the dose should be calculated based on the patient's first body weight of the day.

Table 5 Ceftobiprole dosing regimen for the treatment of neonates and infants with LOS

Gestational age group (weeks)	Post-natal age (days)			
	3 – 13	**14 – 29**	**30 – 59**	**60 – 90**
24 – 26	7.5 mg/kg q12h	7.5 mg/kg q12h	10 mg/kg q12h	10 mg/kg q12h
27 – 31	10 mg/kg q12h	10 mg/kg q12h	10 mg/kg q12h	15 mg/kg q12h*
32 – 36	10 mg/kg q12h	10 mg/kg q12h	15 mg/kg q12h*	15 mg/kg q12h*
≥ 37	15 mg/kg q12h*	15 mg/kg q12h*	15 mg/kg q12h*	15 mg/kg q8h*

Note: All doses will be infused over 2 hours. The maximum allowable dose in adult and pediatric patients is 500 mg regardless of body weight.
* Neonates and infants with a body weight < 4 kg should receive a maximum of 10 mg/kg/dose.

If ampicillin and/or an aminoglycoside are added, these IV solutions must not be mixed with ceftobiprole or administered through the same line as ceftobiprole. For further details, see the Pharmacy Manual.

6.7 Compliance and drug-supply accountability

The Investigator, and a pharmacist or a pharmacist delegate assigned by the Investigator, must maintain records of the delivery of study drug to the site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused product.

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

- Identification of the patient to whom the drug was dispensed
- Principal Investigator name
- Dates, quantity and batch number of the drug dispensed to the patient
- Quantity of the drug remaining

The inventory must be available for inspection by the Sponsor's monitor(s). All supplies, including partially used or empty vials, must be available for checking by the Sponsor's monitor(s) during monitoring visits and at the end of the study.

6.7.1 Drug disposal

Any remaining drug, including empty vials, may be returned to the study supply packaging provider, or may be destroyed at the site on the request of the Sponsor provided the drug destruction is adequately documented.

7 SAFETY

The role of the DSMB in ensuring the protection of patients' safety is described in Section 3.4.

Stopping criteria for individual patients are described in Section 4.4.

7.1 Warnings and precautions

7.1.1 Ceftobiprole

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

Serious and occasionally fatal adverse reactions have been reported in patients receiving beta-lactam antibiotics, including hypersensitivity (anaphylaxis) and *Clostridioides difficile*-associated colitis or pseudomembranous colitis. Seizures have been associated with the use of ceftobiprole, most commonly occurring in patients with pre-existing central nervous system/seizure disorders. Precipitation can occur when ceftobiprole medocaril is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftobiprole medocaril and calcium-containing solutions, except Lactated Ringer's solution for injection, must not be mixed or administered simultaneously in the same intravenous line.

7.1.2 Ampicillin / aminoglycosides

The safety profiles of these standard-of-care antibiotics that may be combined with ceftobiprole at the discretion of the Investigator are well characterised due to their use over many years, and are described in their respective local labels.

Serious or significant adverse reactions that may occur in patients receiving ampicillin include hypersensitivity (anaphylaxis) and *Clostridioides difficile*-associated colitis or pseudomembranous colitis. Concurrent administration of ampicillin and allopurinol increases substantially the incidence of skin rashes.

Aminoglycosides generally have a narrow therapeutic window and therapeutic drug monitoring should be considered in patients treated with aminoglycosides to ensure adequate therapeutic exposure and to avoid toxicity due to overexposure. Relevant adverse reactions include among others hypersensitivity, ototoxicity, nephrotoxicity, impaired neuromuscular transmission, convulsions, and *Clostridioides difficile*-associated colitis or pseudomembranous colitis.

If ampicillin and/or an aminoglycoside are added, these IV solutions must not be mixed with ceftobiprole or administered through the same line as ceftobiprole.

7.1.3 Contraception and pregnancy

Not applicable.

7.2 Definitions

7.2.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigational patient administered a pharmaceutical product that does not necessarily

have a causal relationship with study-drug treatment. An AE can therefore be any unfavourable and unintended sign (for example, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Complications associated with scheduled procedures are considered AEs.

Events that occur following the full execution of the ICF but prior to dosing are discussed in Section 7.4.2.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA), and grouped by System Organ Class and Preferred Term.

7.2.2 Serious adverse event

An SAE is any AE that meets 1 or more of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is classified as an important medical event or medically significant event

Medical and scientific judgement should be exercised in deciding whether an AE should be considered an important medical event (and consequently an SAE). Such events may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient, or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

It should be noted that:

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

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

- Routine treatment not associated with any deterioration in condition
- Elective or planned treatment, including surgical interventions, both related and unrelated to the patient's LOS, if the plan for the respective intervention was documented prior to the first dose of study drug
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the patient's LOS and has not worsened
- Admission to a hospital or other institution for general care, not associated with any deterioration in condition

7.2.3 Adverse drug reaction

In the context of this study protocol, an ADR or serious adverse reaction (SAR) is an AE or SAE respectively for which there is a reasonable possibility that the drug caused the event, i.e., it has been assessed by the Investigator and/or the Sponsor as either *Possibly related* or *Probably related* to the study drug or to ampicillin or an aminoglycoside (see Section 7.3.2).

7.2.4 Suspected unexpected serious adverse reaction

A suspected unexpected serious adverse reaction (SUSAR) is any SAE considered by the Investigator or by the Sponsor to be *Possibly related* or *Probably related* to the study drug or to ampicillin or an aminoglycoside (see Section 7.3.2), which is not listed in the Reference Safety Information applicable at the time of occurrence of the event, or is not listed at the specificity (i.e., nature, outcome) or severity that has been observed.

7.2.5 Adverse events of special interest

An adverse event of special interest (AESI) is defined as a serious or non-serious AE that is of scientific and medical concern specific to the sponsor's product for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. The following are considered AEs of special interest for the purposes of this study, based on nonclinical data and the known safety profile of ceftobiprole or the cephalosporin class of antibiotics. and are to be promptly reported in the eCRF, along with an assessment of relationship by the Investigator:

- Hypersensitivity reactions
- Convulsions
- *Clostridioides difficile*-associated colitis or pseudomembranous colitis
- Hepatic enzyme increased
- Hyponatremia
- Renal failure
- Infusion site reactions
- Thromboembolic events

7.2.6 Further adverse event definitions

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered by the Investigator to be a component of a specific disease or syndrome, it should be recorded as a separate AE.

Laboratory data are to be collected as stipulated in Section 5.5.4. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

7.2.7 Special Situations

Special Situations include overdose, misuse, and medication error. A Special Situation may occur with or without an associated AE.

- ***Overdose:*** Administration of a quantity of a medicinal product once or cumulatively which is above the maximum recommended dose indicated in the authorized product information or administration specification set out in this protocol. Clinical judgement should always be applied when applying this definition.
- ***Misuse of a medicinal product:*** Intentional and inappropriate use of a medicinal product not in accordance with the terms indicated in the authorized product information or administration specification set out in this protocol.
- ***Medication error:*** An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.

7.3 Evaluation of adverse events

7.3.1 Grading of severity

The severity of an AE will be graded on the following scale:

- Mild: no change in baseline age appropriate behaviour*
- Moderate: resulting in minor changes of baseline age-appropriate behaviour
- Severe: resulting in major changes of baseline age-appropriate behaviour* and/or non-life threatening changes in basal physiological processes**
- Life-threatening
- Fatal

* Age-appropriate behaviour refers to oral feeding behaviour, voluntary movements and activity, crying pattern, social interactions and perception of pain

** Basal physiological processes refer to oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning

7.3.2 Assessment of causality

The relationship between an AE and the study drug will be determined by the Investigator on the basis of their clinical judgement and the following definitions.

To align with the binary causality assessment required for clinical studies, based on the Investigator's evaluations, the cases will be categorised as:

- Unrelated: when evaluated as *Unlikely related* or *Not related* to the study drug or to ampicillin or an aminoglycoside
- Related: when evaluated as *Probably related* or *Possibly related* to the study drug or to ampicillin or an aminoglycoside

UNRELATED

This category comprises events that are either

- ***Not related*** to the study drug or to ampicillin or an aminoglycoside, i.e., clearly and incontrovertibly due only to extraneous causes such as the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient, or
- ***Unlikely related*** to the study drug or to ampicillin or an aminoglycoside, i.e., the event may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient

An AE is also categorised as *Unlikely related / Not related* if it does not follow a reasonable temporal sequence from administration of the study drug or ampicillin and/or an aminoglycoside, i.e., based on the time between the administration of study drug and occurrence of the event, a relationship is not plausible.

Examples for the absence of a reasonable temporal sequence from administration of the study drug are that the drug was:

- Re-administered, and the event did not recur, or
- Interrupted or stopped, and the event did not improve or disappear

Finally, an AE may be assessed to be *Not related / Unlikely related* if it does not follow a known pattern of the response to the study drug or drugs of the same substance class.

RELATED

Probably related

This category is applicable to an AE that is considered, with a high degree of certainty, to be related to the study drug or to ampicillin and/or an aminoglycoside (i.e., this category also comprises events that are definitely related to the study drug).

An AE event may be considered (at least) *Probably related* (or considered definitely related) to the study drug or ampicillin and/or an aminoglycoside if it meets one or more of the following criteria:

- It follows a reasonable temporal sequence from administration of the study drug or ampicillin and/or an aminoglycoside, i.e., based on the time between the administration of study drug and the occurrence of the event, a relationship is plausible, e.g.,
  - The drug was interrupted or stopped, and the event improved or disappeared
  - The drug was re-administered, and the event recurred

- It follows a known pattern of the response to the suspected drug or drugs of the same substance class
- It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient

Possibly related

An AE may be considered to be (at least) *Possibly related* to the study drug or treatment with ampicillin and/or an aminoglycoside if:

- It follows a reasonable temporal sequence from administration of the study drug or ampicillin and/or an aminoglycoside (see also additional explanations above), or it follows a known pattern of the response to the suspected drug or drugs of the same substance class; or
- It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or
- It does not follow a plausible temporal relationship or a known pattern of response but there is no alternative explanation for the event.

7.4 Handling of safety information and collection periods

7.4.1 Responsibilities and procedures

The responsibility for the safety of an individual patient lies in all cases with the Investigator. This includes the timely review of all safety data obtained during the course of the study.

An Investigator must instruct the parent(s) or LAR to report any AEs the patient experiences.

7.4.2 Handling of safety data during the pre-treatment period

Any relevant change in, or worsening of, a patient's condition occurring after execution of the study ICF but prior to dosing, is to be recorded in the medical history page of the eCRF (see Section 5.3.1), unless the occurrence is assessed as related to the study procedure, in which case it must be recorded in the AE page. If the event is assessed as both serious (see Section 7.2.2) and related to study-specific procedures, it must be reported to the Sponsor's safety representative, using the same procedures as for an SAE (see Section 7.4.3.2).

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

From the start of first dosing up to and including the LFU visit 28−35 days after the last study drug administration, any change in, or worsening of, a patient's condition, all AEs, and Special Situations must be collected and reported in the eCRF (See Section 9.1.2). SAEs must in addition be reported and recorded on the SAE form (see Section 7.4.3.2).

7.4.3.1 Reporting procedures for adverse events that do not meet seriousness criteria

All AEs directly observed (physical examination, laboratory test, or other assessments), mentioned by the parent(s) or LAR, or reported by the parent(s) or LAR upon non-directive questioning, must be recorded on the AE pages of the eCRF in the English language, and should include the following information:

- The term identifying the event. If possible, a diagnosis should be documented rather than signs and symptoms, using self-explanatory and concise medical terminology. If an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Note that disease progression is considered an efficacy outcome parameter, and should not be recorded as an AE unless the outcome is death.
- Duration (start and end dates)
- Grading of severity (see Section 7.2.3)
- Relationship to study drug (causality assessment) (see Section 7.3.2)
- Action taken in regard to study drug or ampicillin and/or an aminoglycoside or any suspected concomitant medication
- Additional treatments given for the event
- Whether the event is an SAE (seriousness assessment) (see Section 7.2.2)
- Outcome

Further details on completing the relevant pages in the eCRF are provided in the eCRF completion guidelines. In addition, concomitant medications (with start and stop dates) and medical history should be updated as needed.

Abnormal laboratory results should not be recorded as an AE unless the abnormal result meets 1 or more of the following criteria:

- Induces clinical signs or symptoms which require therapy or additional diagnostic evaluation
- Requires study drug dose modification or discontinuation
- Is considered clinically significant

If a laboratory abnormality meets 1 of the above criteria, the clinical syndrome associated with the laboratory abnormality is to be recorded (e.g., diabetes mellitus instead of hyperglycemia).

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

7.4.3.2 Reporting procedures for serious adverse events

7.4.3.2.1 Investigator's responsibility

In addition to being reported and followed up as AEs (see Section 7.4), events which are classified as SAEs, must be reported to the Sponsor's safety representative listed below, within 24 hours of awareness of the event.

In addition to completion of the SAE form, such reports may include detailed anonymised descriptions (e.g., discharge letter, autopsy report) and/or relevant data (e.g., ECG, laboratory tests, discharge summaries, post-mortem results). If any questions arise, the Sponsor's medical monitor or designee should be consulted.

The information provided in an SAE form should be as complete as possible, but must at a minimum include the following:

- The diagnosis / short description of the AE, and the reason for categorising the AE as serious
- Patient ID and treatment (if applicable)
- Investigator's name and phone number (if applicable)
- Name of the suspect study drug or ampicillin or an aminoglycoside and dates of administration
- Assessment of causality

If all information about the event is not yet known, the Investigator will be required to report any additional information within 24 hours, and further information as it becomes available.

The Investigator or designee must notify the applicable IEC/IRB of the event in line with local requirements.

7.4.3.2.2 Sponsor's responsibilities

The Sponsor must ensure the reporting of SUSARs and any expeditable SAEs to Health Authorities and IECs/IRBs in accordance with applicable laws and regulations.

In the event of a SUSAR, the Sponsor must ensure that Investigators active in any other interventional studies with the study drug for which it is the Sponsor are informed.

Expectedness of SAEs for regulatory expedited reporting will be assessed by the Sponsor against the applicable Reference Safety Information of the study drug; for ceftobiprole, the Reference Safety Information is found in the IB in effect at the time of onset of the event.

7.4.4 Follow-up of adverse events

Once an AE is detected, it must be proactively followed at each visit (or more frequently if necessary) for any changes in severity, relationship to the study drug, interventions required for treatment, and the event's outcome.

All AEs must be followed up until they have returned to baseline status or resolved to Grade 1, have stabilised, or until the scheduled LFU visit.

Unresolved ADRs, SARs, and unrelated SAEs at the time of the LFU visit must be followed up until they have, in the opinion of the Investigator, resolved to baseline, Grade 1, stabilised, or are deemed to be irreversible (including death), or until the parent(s) or LAR withdraw their consent.

7.4.5 Handling of post-study safety data

After the LFU visit, only SARs should be collected and reported; however, these events are not captured in the eCRF.

New SARs that occur after the LFU visit will be followed until they have, in the opinion of the Investigator, resolved to baseline, stabilised, or are deemed to be irreversible (including death), or until the parent(s) or LAR withdraw their consent for participation of the patient in the study.

7.4.6 Reporting and handling of pregnancies

Not applicable.

7.5 Adverse events associated with an overdose or any other Special Situation

Any overdose or any other Special Situation (with or without an AE) should be recorded in the eCRF.

All AEs associated with an overdose or medication error should be recorded on the eCRF (see Section 9.1.2). If the associated AE is assessed as an SAE, the event should be reported to the Sponsor immediately (see Section 7.4.3.2).

8 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Details of the statistical analyses presented below will be provided in the SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalised prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

8.1 Study endpoints

8.1.1 Primary endpoint

The primary endpoint is safety and tolerability in the Safety population, as assessed by AEs, SAEs, deaths, and discontinuations due to AEs during treatment with ceftobiprole and at the EOT, TOC, and LFU visits, as well as clinical laboratory tests, vital signs, and physical examination findings.

8.1.2 Secondary endpoints

Pharmacokinetics

- Plasma levels of ceftobiprole, ceftobiprole medocaril, and open-ring metabolite in the PK population

Efficacy

- Clinical cure rate at the EOT and TOC visits (ITT and CE populations)
- All-cause mortality through Day 28 (ITT population)
- Microbiological eradication or presumed eradication rate at the EOT and TOC visits (mITT and ME populations)
- Improved signs and symptoms of LOS at the Day 3, EOT, and TOC visits (ITT and CE populations)

8.2 Analysis populations

The following analysis populations are defined for this study:

8.2.1 Intent-to-treat (ITT) population / Safety population

All patients enrolled in the study who received at least one dose of ceftobiprole.

8.2.2 Clinically Evaluable (CE) population

Patients in the ITT population who received at least 48 hours of study treatment (i.e., four or six infusions of ceftobiprole as applicable) and had a completed overall clinical outcome assessment at the TOC visit, no major protocol deviations, and no concomitant systemic non-study antibiotic therapy.

8.2.3 Microbiological Intent-to-treat (mITT) population

All patients in the ITT population with a valid pathogen identified at baseline.

8.2.4 Microbiologically Evaluable (ME) population

All patients in the CE analysis population with a valid pathogen identified at baseline and a microbiological outcome assessment at the TOC visit.

8.2.5 Pharmacokinetics (PK) population

All patients who received ceftobiprole and had at least one sample of plasma concentration measurement obtained by the appropriate methodology.

8.3 Sample size considerations

The study is not powered for inferential statistical analysis. The sample size (eight patients; two term and six pre-term) is considered adequate to evaluate the safety of ceftobiprole in neonates and young infants with LOS.

8.4 Statistical and analytical methods

There will be no formal hypothesis testing in this study. Descriptive statistics will be applied to the primary and secondary endpoints as follows: number, mean, standard deviation, median, minimum, and maximum will be provided for continuous variables, and frequency distributions (counts and percentages) will be shown for categorical variables. All variables will be summarised overall and by gestational and post-natal ages as appropriate. Variables may be compared to baseline where applicable. Listings of individual patients' data will also be produced.

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

8.4.1 Primary endpoint analysis

8.4.1.1 Safety/tolerability analysis

Safety will be assessed through summaries of AEs, clinical laboratory tests, vital signs, and physical examination findings. All safety analyses will be based on the Safety population.

The incidence of AEs and SAEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT), and by severity, relationship to treatment, and outcome. Tables of AEs leading to study drug discontinuation and withdrawal from the study will also be provided.

Adverse occurrences (as defined in Section 7.2) will be provided in a listing.

Descriptive statistics summarising local laboratory data will be presented by study visit. The change from baseline to each post-baseline visit and to the overall worst post-baseline value will also be summarised.

Descriptive statistics of vital signs will be presented by study visit, as well as the change from baseline at each study visit. The percentage of abnormalities in the physical examination will be presented by study visit.

8.4.2 Secondary endpoint analyses

8.4.2.1 Pharmacokinetic analysis

Descriptive summary statistics of plasma concentrations of ceftobiprole, ceftobiprole medocaril, and open-ring metabolite in the PK population will be presented by timepoint and by gestational and post-natal ages. Population PK modelling, Monte Carlo simulations, and PK-PD analyses will be reported separately.

8.4.2.2 Efficacy analyses

The following efficacy assessments will be analysed using descriptive statistics:

- Clinical and microbiological outcome assessments at the EOT and TOC visits (clinical outcomes in the ITT and CE populations; microbiological outcomes in the mITT and ME populations)
- All-cause mortality through Day 28 (ITT population)
- Signs and symptoms of LOS at the Day 3, EOT and TOC visits (ITT and CE populations)

8.4.3 Study drug exposure and compliance

The actual dose, duration in days, and compliance of the study drug will be listed by patient and summarised through descriptive statistics in the safety population.

8.4.4 Prior and concomitant treatments

Medications and significant non-drug therapies used prior to and after the start of the study drug will be listed by patient and summarised by Anatomical Therapeutic Chemical term and Preferred Term.

8.4.5 Handling of missing data and discontinuations

Missing data will not be imputed. Patients whose clinical response is unknown or not reported will be treated as non-responders.

Reasons for discontinuation and the date of discontinuation will be listed.

9 STUDY ADMINISTRATION AND REGULATORY ASPECTS

9.1 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.

9.1.1 Investigator Site File

The ISF must contain all essential documents as required by International Council for Harmonisation (ICH) E6 and applicable regulations, including the IB, this protocol and any subsequent amendments, eCRFs, Query Forms, documented IEC/IRB approvals, documented regulatory approvals, sample ICFs, drug records, staff curriculum vitae, and other appropriate documents/correspondence.

9.1.2 Case report forms

For each patient enrolled in the study, including patients who do not complete the study and patients for whom an eCRF is initiated during Screening but who are not dosed, an eCRF must be completed and signed by the Investigator or authorised site staff. If a patient discontinues from the study, the reason must be noted on the eCRF. If a patient is discontinued from the study because of an 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 clearly documented.

9.1.3 Patient source documents

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

9.1.4 Document retention and archiving

The Investigator must keep all study documents on file for at least 25 years after completion or discontinuation of the study, unless otherwise required by applicable laws or regulations. Subsequently, the Sponsor will inform the Investigator when the study documents can be destroyed, subject to applicable regulations.

These files must be made available for audits and inspection, upon reasonable request, to the authorised representative of the Sponsor, or to Health Authorities.

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 the archiving requirement at the study site for any or all of the study documents, arrangements must be made between the Investigator and the Sponsor for appropriate storage.

9.2 Clinical monitoring

Before study initiation, at a site initiation visit, the Sponsor will review the protocol, eCRFs and other study documentation with the Investigators and the site staff.

The monitor must visit the Investigator and the study facilities on a regular basis throughout the study to verify adherence to GCP and this protocol, and the completeness, consistency and accuracy of the data being entered in the eCRFs. The monitor must also ensure that the study drug is being stored, dispensed, and accounted for in accordance with specifications.

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 patient records needed to verify the entries in the eCRFs.

The Investigator must cooperate with the monitor to ensure that any protocol deviations or other issues detected in the course of monitoring visits are resolved.

Monitoring reports must be written after each monitoring visit, per site and per visit. These monitoring reports must be reviewed and approved by the respective supervisors of the Monitors.

Further monitoring instructions are provided in the Monitoring Plan.

9.3 Audits and inspections

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

9.4 Protocol amendments

Protocol amendments must be prepared by a representative of the Sponsor, and be reviewed and approved in accordance with the Sponsor's Standard Operating Procedures (SOPs).

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

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

9.5 Premature termination of the study

The Sponsor reserves the right to terminate the study at any time (see Section 4.6). An Investigator has the right to terminate his or her participation in the study at any time. Should either of these events occur, both parties will arrange the necessary procedures after review and consultation.

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

9.6 Publication policy

The Sponsor is committed to registering this study in a publicly accessible clinical trial registry (e.g., www.clinicaltrials.gov), and will ensure that the results of this study will be made available to the medical community consistent with the ICH GCP guidelines, the Sponsor's SOPs, applicable laws and regulations, and the Good Publication Practice (GPP3) guidelines.

The Sponsor will prepare a clinical study report for submission to Health Authorities providing the results of all planned analyses within 6 months after the end of the study.

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, submission of an abstract

and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing study results.

These timelines may be extended if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the clinical study report, subject to applicable confidentiality agreements.

When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and SAP to facilitate peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal to post on its website the key sections of the protocol that are relevant to evaluating the study, specifically including those sections describing the study objectives and hypotheses, the inclusion and exclusion criteria, the study design and procedures, the efficacy and safety measures, the SAP, and any relevant protocol amendments. The Sponsor reserves the right to redact proprietary information from these documents.

As this is a multicenter study, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an Investigator and his or her colleagues may publish their data independently. The limitations of single study site observations in a multicenter study should always be described in such a manuscript.

Authorship credit and related decisions in regard to publication of the results of this study will comply with the GPP3 guidelines.

The Sponsor retains the right to review all proposed abstracts, manuscripts, or presentations regarding this study 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

10 ETHICS AND GOOD CLINICAL PRACTICE

10.1 Good clinical practice

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

10.2 Informed consent

Eligible patients may only be enrolled in the study after their parent(s) or LAR provide written IEC/IRB-approved informed consent. Written informed consent must be obtained by the Investigator or designee prior to initiation of any study procedures. In the event of an emergency, verbal consent is acceptable, followed by written informed consent as soon as the situation allows.

The procedure for obtaining informed consent for each individual participating in this study, must include adequate explanation of the aims, methods, objectives and potential

risks of the study. It must also be explained to parents or LARs that they are completely free to refuse to enter the study, or to withdraw from the study at any time for any reason.

Written consent must be witnessed and countersigned by the Investigator or a qualified designee, as appropriate. In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and GCP as outlined in ICH Guideline E6 and other relevant guidelines, and the ethical principles having their origin in the Declaration of Helsinki.

Copies of signed ICFs must be given to the parent(s) or LAR, and the originals filed at the study site.

In the event that the parent(s) or LAR are temporarily unable or unavailable to sign the consent document, an impartial witness must be present during the entire informed consent discussion. After the parent(s) or LAR have verbally consented to participation in the study, the witness's signature must be obtained on the form to attest that the information in the ICF was accurately explained, and was understood by the parent(s) or LAR.

The eCRFs for this study contain a section for documenting the parents' or LAR's informed consent, and this must be completed appropriately. If new safety information results in significant changes in the benefit-risk assessment for ceftobiprole, the ICF must be reviewed and updated. All parents or LARs of patients currently enrolled in the study who have not yet completed the treatment or post-treatment phases must be given the new information and a copy of the revised ICF, and asked to give their consent to the patient continuing in the study.

10.3 Patient confidentiality and data protection

The Investigator must ensure that patient anonymity is maintained, and that patients' identities are protected from unauthorised parties. This includes any electronic data generated during the study. In the eCRF, or other documents submitted to the Sponsor, patients must be identified only by an identification code, and not by name. The Investigator must keep a confidential patient identification code list, as described in Section 8.3.21 of ICH Guideline E6. The Sponsor is responsible for ensuring compliance with all applicable data protection laws.

10.4 Independent Ethics Committees / Institutional Review Boards

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

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

11 PROTOCOL VERSION HISTORY

Date	Version	Summary of changes
16 May 2022	1.0	–
24 May 2022	2.0	• Addition of the definition of the end of the study • Addition of adverse events of special interest • Correction of the timeline for preparation of the clinical study report
11 July 2022	3.0	• Deletion of Section 9.2 Biological sample and bacterial isolate retention
20 July 2022	4.0	• Updated dose rationale in Section 1.4.3. • Addition of the option in some circumstances that treatment with ceftobiprole may be stopped after 5 days at the discretion of the Investigator. • Clarification that in Inclusion criterion 3, clinical criterion (i), references to hypotonia are to muscular or arterial hypotonia. • Addition to Inclusion criterion 3 laboratory criterion (d), Interleukin-6 elevated according to local laboratory thresholds. • Clarification that for the purposes of Exclusion criterion 4, the patient must have proven ventilator-associated pneumonia. • Change of the duration of systemic antibacterial therapy within 7 days before start of study medication from 48 to 72 hours for the purposes of Exclusion criterion 12. • Clarification that during the active treatment period, vital signs must be recorded within 30 minutes before the first study drug administration, and then three times daily. • Section 7.2.7 has been amended to ensure that Special Situations are applicable to a patient population aged from ≥ 3 days to ≤ 3 months. • Addition of two categories to the grading of the severity of adverse events. • Section 7.4.2 has been amended to clarify the recording and reporting requirements for events occurring after execution of the study ICF but prior to dosing.
9 July 2024	5.0	• Amendment of the planned study population to require at least eight patients, comprising at least two term neonates and six pre-term neonates. • Reduction of the expected minimum treatment duration from 7 days to 3 days. • Clarification of inclusion criterion ‘hypotonia’ by removing ‘arterial’ from inclusion criterion 3(i)

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13 APPENDICES

Appendix 1 Renal function

For assessment of renal function, serum creatinine is typically used after the first week of life in term neonates and after 4 weeks in pre-term neonates. Before then, intra-individual changes (related to post-menstrual age) in serum creatinine are used as a guide to renal function.

In addition, the following references should be considered:

- Schwartz and colleagues (Schwartz 2009) published the following modified formula (based on serum creatinine levels determined with the enzymatic method):

  Estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2) = 0.413 • length (cm) / creatinine (mg/dL).
- Abitbol and colleagues (Abitbol 2014) reported serum creatinine levels of 0.68 ± 0.14 mg/dL during post-natal days 3–7 in 60 pre-term neonates (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 > 20 mL/min/1.73 m^2. Of note, the creatinine-based equation underestimated the GFR compared to the CysC-based equations, especially in pre-term neonates.
- Two graphs presented at an EMA Workshop on regulatory and scientific issues related to the investigation of medicinal products intended for neonate use (Van den Anker 2006) indicated that serum creatinine levels in neonates with a body weight > 1000 g, or a gestational age > 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 (CHMP-PDCO 2009). Glomerular filtration rate (GFR) is indirectly proportional to serum creatinine, i.e., a GFR of two-thirds of normal corresponds to a 1.5-fold greater than normal serum creatinine level. Since post-menstrual age 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 7:

Post-menstrual age (weeks)	Creatinine (mg/dL)	Rationale
28 – 34 completed	1.32	150% of the upper limit of the laboratory normal ranges
35 – 42 completed	1.10	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

Considering these serum 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/1.73 m^2)		
	Post-menstrual age (weeks)		
	28 – 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 7 to potential participants in the study.

Appendix 2 Investigator's protocol signature page

BASILEA
INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol	BPR-PIP-003	Basilea product:	Ceftobiprole medocaril
Protocol title:	**A multicenter open-label, single-arm, multiple-dose study to evaluate the safety, pharmacokinetics, and efficacy of ceftobiprole medocaril in term and pre-term neonates and infants up to 3 months of age with late-onset sepsis**		
Sponsor:	Basilea Pharmaceutica International Ltd, Allschwil		
Date / Version:	9 July 2024 / Version 5.0		
Name of Principal Investigator:			
Study site:			

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

I agree to follow International Council for Harmonisation (ICH) guidelines for good clinical practice (GCP), and specifically, to obtain approval from the applicable Independent Ethics Committee / Institutional Review Board prior to study start, allow direct access to source documents, and agree to inspection by auditors from the Sponsor and regulatory authorities. I will ensure that the investigational product(s) supplied by the Sponsor will be used only as described in the protocol for this study, and I acknowledge that if any other use is desired, written permission must be obtained from the Sponsor.

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

Please print name and date next to the signature

Signature	**Name**	**Date**
	Principal Investigator	