NCT05856227

STATISTICAL ANALYSIS PLAN

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

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LIST OF ABBREVIATIONS

ACM	All-cause mortality
AE	Adverse event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
CE	Clinically Evaluable
DSMB	Data and Safety Monitoring Board
eCRF	Electronic CRF
EOT	End-of-treatment
ITT	Intent-to-treat
IV	Intravenous
LFU	Last follow-up
LOS	Late-onset sepsis
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Microbiological Intent-to-treat
PK	Pharmacokinetic(s)
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TOC	Test-of-cure
WHO DDE	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION

This document outlines the statistical methods to be implemented in the analysis of data collected within the scope of Basilea Pharmaceutica International Ltd., Allschwil, 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).

The purpose of this Statistical Analysis Plan (SAP) is to define the planned statistical methods in line with the study objectives. This plan should be read in conjunction with the study protocol (Version 5.0, dated 9 July 2024 at the time of finalization). All analyses will be conducted using SAS® Version 9.4 or higher.

2 OBJECTIVES

2.1 Primary objective

The primary objective of study BPR-PIP-003 is to characterize 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).

2.2 Secondary objectives

The secondary objectives are 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 (ACM)
- Microbiological response.

3 INVESTIGATIONAL PLAN

3.1 Overall study design

3.1.1 Brief summary

This is a multicenter, open-label, single-arm, multiple-dose study of intravenous (IV) ceftobiprole in term and pre-term neonates and infants up to 3 months of age with LOS.

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 judgment, 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, test-of-cure (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.

An overview of the study design is provided in protocol Section 3. The schedule of assessments and procedures for the different periods are provided in protocol Section 5.1.

An independent Data and Safety Monitoring Board (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, as specified in the DSMB Charter.

3.1.2 Number of patients

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

3.1.3 Treatments

Eligible patients will receive ceftobiprole as a 2-hour IV infusion according to the schedule in Table 1, 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 1 Ceftobiprole dosing regimen for the treatment of neonates and infants with late-onset sepsis

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.

3.2 Study endpoints

3.2.1 Primary endpoints

The primary endpoint is safety and tolerability in the Safety population, as assessed by adverse events (AEs), serious adverse events (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

The pharmacokinetics secondary endpoints are:

- Plasma levels of ceftobiprole, ceftobiprole medocaril, and open-ring metabolite (PK population).

The efficacy secondary endpoints are:

- Clinical cure rate at the EOT and TOC visits [Intent-to-treat (ITT) and Clinically Evaluable (CE) populations]
- ACM through Day 28 (ITT population)
- Microbiological eradication or presumed eradication rate at the EOT and TOC visits (Microbiological Intent-to-treat (mITT) and Microbiologically Evaluable (ME) populations)
- Improved signs and symptoms of LOS at the Day 3, EOT, and TOC visits (ITT and CE populations).

4 GENERAL STATISTICAL CONSIDERATIONS

Summary outputs, where possible, will be presented by neonate groups (term and pre-term) and overall. No formal hypothesis testing will be performed. Continuous data will be described using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Categorical data will be described using the patient count and percentage in each category. Non-zero percentages will be rounded to one decimal place, except 100%, which will be displayed without any decimal places. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported, up to a maximum of three decimal places. Mean and median will be displayed to one level of precision greater than the data collected, up to a maximum of three decimal places. Standard deviation will be displayed to two levels of precision greater than the data collected, up to a maximum of three decimal places.

When count data are presented, the percentage will be suppressed when the count is zero, to draw attention to the non-zero counts. A row denoted ‘Missing’ will be included in count tabulations where specified in the table shells, to account for dropouts and missing values. The denominator for all percentages will be the number of patients in the population of interest, unless otherwise specified.

All data will be displayed in listings sorted by neonate groups (term and pre-term) and subject ID.

4.1 Sample size justification

This 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 infants aged ≤ 3 months with LOS.

4.2 Analysis populations

4.2.1 Intent-to-treat population / Safety population

The Intent-to-treat (ITT) / Safety population consists of all enrolled patients who received at least one dose of ceftobiprole.

4.2.2 Clinically Evaluable population

The Clinically Evaluable (CE) population consists of patients in the ITT population who received at least 48 hours of study drug and had a completed overall clinical outcome assessment at the TOC visit, no major protocol deviations, and no concomitant systemic non-study antibiotic therapy.

4.2.3 Microbiological Intent-to-treat population

The mITT population consists of all patients in the ITT population with a causative pathogen identified at baseline.

4.2.4 Microbiologically Evaluable population

The ME population consists of all patients in the CE population with a causative pathogen identified at baseline and a microbiological outcome assessment at the TOC visit.

4.2.5 Pharmacokinetic population

The PK population consists of 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.

4.3 Other important considerations

4.3.1 Definition of baseline

Unless otherwise specified, baseline is defined as the last non-missing assessment prior to the first study drug administration. Both scheduled and unscheduled visits and assessments will be used in determining baseline.

4.3.2 Definition of infecting organism (i.e., pathogen)

The identification of organisms as infecting (i.e., pathogen) or non-infecting is based on Investigator assessment as reported in the eCRF. The assessment may be based on blood samples, urine, cerebrospinal fluid, or any other suitable specimen samples.

When multiple samples from the same specimen are taken on a specific study day and isolates are not all sent for central microbiology testing, or when local and central identification differ, only the results from the central microbiology laboratory on that study day will be considered for the identification of organisms.

A causative pathogen is an infecting organism confirmed by central identification.

4.3.3 Study day calculation and visit windows

Visit windowing approaches will not be used for this study, and visit-based summaries will include scheduled assessments only. If more than the specified number of measurements has been taken in a scheduled visit, the latest recorded values will be used in visit summaries, unless otherwise stated. All scheduled and unscheduled post-baseline assessments will be used for derivation of minimum and maximum post-baseline values. If more than one assessment has the same minimum or maximum value, then the record with earliest occurrence will be selected respectively as the minimum or maximum assessment.

The following conventions will be used to calculate analysis study day:

- Day 1 is the day of first study drug administration. Day −1 is the day before Day 1. No Day 0 is defined for this study.
- Prior to Day 1, the algorithm is:
  Study Day = visit/examination date − date of first study drug administration
- For Day 1 and subsequent days, the algorithm is:
  Study Day = visit/examination date − date of first study drug administration + 1.

Summary data such as AEs and concomitant medications will not be reported by visit. Tables that report abnormalities (e.g., clinically-notable abnormalities, laboratory shift tables) will include all assessments.

4.3.4 Missing and partial data

The following rules for missing data will be followed:

- Adverse event and prior/concomitant medication date imputations will follow the rules described in Appendix 1.
- The causality assessment for AEs should not be missing and will be queried for a value. Adverse events with missing causality will be considered related to study drug.
- For ACM through Day 28, patients with unknown survival status will be considered deceased for the efficacy outcome. If it is known that the patient died but death date is unknown, then the death date will be imputed to last date known to be alive +1 day.
- Unless otherwise specified, missing values for other individual data points will remain as missing. Missing values will not be imputed, and only observed values will be used in data analyses and presentation.

4.3.5 Duration (e.g., for adverse events)

If date and time are collected, then duration is calculated as event end date and time minus event onset date and time. Duration will be displayed as days and fractions of days, or as hours and fractions of hours, as appropriate.

If only the date is collected, then the duration in days is calculated as event end date minus event onset date + 1.

4.3.6 Coding dictionaries

Adverse events and medical history are to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 or later. Previous and concomitant treatments are to be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE) dated 01MAR2024 or later (format B3).

5 PATIENT DISPOSITION

5.1 Disposition

The following analysis sets will be summarized: patients in the ITT/Safety population, patients enrolled but never dosed, patients in the CE population, patients in the mITT population, patients in the ME population, and patients in the PK population. All percentages will be based on the number of patients in the ITT population. Patients who failed screening, and the reasons for screen failure, will be listed only.

Patient disposition (treatment, EOT, TOC, and LFU) will be summarized for the ITT population.

5.2 Protocol deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The protocol deviations will be categorized as important and non-important deviations, with important deviations further classified as major or minor (see the definition of the CE population in Section 4.2.2).

All protocol deviations will be listed, with patients with major protocol deviations leading to exclusion from CE population identified prior to database lock.

5.3 Inclusion and exclusion criteria

Full inclusion and exclusion criteria are listed in protocol Section 4.2 and 4.3, respectively. Data for inclusion/exclusion criteria for each patient will be listed.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1 Demographics and general baseline characteristics

The following demographics and baseline characteristics data will be presented in tables using descriptive statistics for the ITT, CE, mITT, and PK populations:

- Post-natal age, gestational age, breastfed by lactating mother status, sex, race, ethnicity
- Height, weight.

6.2 Medical history

Medical history will be summarized overall and for each System Organ Class (SOC) and Preferred Term (PT), for the ITT population.

7 TREATMENTS AND MEDICATIONS

7.1 Prior and concomitant medications

All medications, other than the study drug, used during the study (from 7 days prior to the first dose of study drug, or from 3 days prior to the first dose of study drug for medications taken by the lactating mother), must be documented on the appropriate section of the eCRF.

Prior medications are defined as medications with a stop date prior to the first dose of study drug. Concomitant medications are defined as medications that are either ongoing at the time of the first dose of study drug, or start after the first dose of study drug.

The number and percentage of patients who receive prior and/or concomitant medication will be summarized separately by ATC level 2, ATC level 4, and PT.

At each level of summarization, a patient is counted once if he/she reports one or more medications at that level. All prior medications and concomitant medications will be summarized for the ITT population.

The imputation algorithm for partial concomitant medication dates is provided in Appendix 1.

7.2 Concomitant procedures

Concomitant procedures are defined as procedures that are either ongoing on the time of the first dose of study drug, or with a start date missing, or start after the first dose of study drug. All concomitant procedures will be listed.

7.3 Study treatments

7.3.1 Study drug exposure

Duration of study drug therapy and compliance will be summarized for the Safety population.

- Study drug duration is defined as:

  Days of (Date and time of the last dose – Date and time of first dose), rounded to one decimal.

- Compliance is defined as:

  Actual total dose (mg) / Planned total dose (mg)

Compliance will be classified into one of the categories < 80%, 80–120%, or > 120%, and will be presented as the number and percentage of patients in each category for the Safety population.

7.3.2 Study drug administration

All study drug administration data will be listed.

8 EFFICACY ANALYSIS

8.1 Overall clinical outcome

Overall clinical outcome is to be assessed at the EOT and TOC visits by the Investigator as 'Clinical cure', 'Clinical failure', or 'Unevaluable' (see protocol Section 5.6.1 for details). Clinical cure rate and reasons for failure or unavailability of data will be summarized in a table for the ITT and CE populations.

8.2 All-cause mortality through Day 28

Vital status is to be assessed at the LFU visit, in person or by telephone contact. Patients will be considered to have died at Day 28 if they meet all the following criteria:

- A death is reported on the eCRF
- The study day for death is ≤ 28.

The ACM at Day 28 will be summarized in a table for the ITT population.

8.3 Microbiological response

Microbiological outcome is to be assessed at the EOT and TOC visits by the Investigator as 'Eradication', 'Presumed eradication', 'Persistence', 'Presumed persistence', 'Unevaluable', or 'Relapse' (see protocol Section 5.6.3 for details). If applicable, the relapse status of the patient is to be assessed at the LFU visit, by the Investigator.

Patients will be considered to have experienced microbiological eradication if they are classified as 'Eradication' or 'Presumed eradication'. Microbiological eradication at EOT and TOC, and relapse status at the LFU visit, will be summarized in a table for the mITT and ME populations.

All microbiological data will be listed.

8.4 Signs and symptoms of late-onset sepsis

Signs and symptoms of LOS are to be assessed by the Investigator as 'Present', 'Absent', 'Improved', 'Unchanged', or 'Worsened'.

Overall signs and symptoms assessment will be derived and summarized at Day 3, EOT, and TOC, for the ITT and CE populations. The following rules will be applied for categorization:

1. Each post-baseline sign or symptom evaluation is re-classified as stated in the following table:

	Post-baseline				
Baseline	Present	Absent	Improved	Unchanged	Worsened
Present	Unchanged	Resolved	Improved	Unchanged	Worsened
Absent	Worsened	Absent	NA	Absent	Worsened

2. Overall assessment for each visit is derived as follows:

- Resolved: all signs and symptoms are classified as ‘Resolved’ or ‘Absent’ (see table above).
- Improved: all signs and symptoms are classified as ‘Resolved’ or ‘Improved’ or ‘Absent’ (see table above), with at least one ‘Improved’.
- Unchanged: all signs and symptoms are classified as ‘Resolved’, ‘Improved’ or 'Unchanged’ or ‘Absent’ (see table above), with at least one ‘Unchanged’.
- Worsened: there is at least one sign or symptom classified as ‘Worsened’.

All signs and symptoms data will be listed.

9 SAFETY ANALYSIS

All Safety analyses will be conducted using the Safety population.

9.1 Adverse events

Adverse events are defined in protocol Section 7.2. As the definition includes only events which occur after first study-drug administration, all AEs are considered to be ‘treatment emergent’. Pre-treatment events are reported as medical history. Relationship and action taken referring to ampicillin and aminoglycoside are listed only.

An overview summary of number and percentage of patients will be provided for any AE, study-drug-related AEs, SAEs, study-drug-related SAEs, AEs leading to treatment discontinuation, study-drug-related AEs leading to treatment discontinuation, AEs leading to treatment interruption / dose reduction, study-drug-related AEs leading to treatment interruption / dose reduction, AEs leading to death, study-drug-related AEs leading to death, AEs of special interest (see Section 9.1.4), and study-drug-related AEs of special interest will be provided.

All AEs, SAEs, and AEs leading to death will be presented in separate listings.

9.1.1 Incidence of adverse events

The number and percentage of patients reporting AEs will be tabulated by SOC and PT for all AEs, and separately for study-drug-related AEs. Patients with multiple events will be counted only once within each category. SOC and PT will be sorted in descending order of frequency in the total of all treatment groups.

In addition, the following categories will be summarized similarly:

- AEs up to EOT visit
- AEs up to TOC visit
- SAEs
- AEs leading to treatment discontinuation
- AEs leading to treatment interruption / dose reduction.

9.1.2 Relationship of adverse events to study drug

The relationship to ceftobiprole is collected based on the possibility that the study drug caused the event. The possible relationships are 'Not Related', 'Unlikely', 'Possible', 'Probable', and 'Not Applicable', with AEs assessed as 'Possible' or 'Probable' classified as study-drug-related.

A summary of AEs will also be presented by relationship to study drug, SOC and PT. If a patient reports multiple occurrences of the same AE, only the worst relationship category will be counted.

Adverse events that are missing an assessment of relationship to study drug will be counted in the study-drug-related AEs summary table, but will be presented in the summary table by relationship and in listing with a 'Missing' relationship.

9.1.3 Severity of adverse event

Severity of AEs is collected in the eCRF as 'Mild', 'Moderate', or 'Severe', and a summary of AEs by severity will be presented in a table. If a patient reports multiple occurrences of the same AE, only the most severe will be counted. AEs that are missing severity will be presented in tables as severity 'Unknown'.

9.1.4 Adverse events of special interest

Adverse events of special interest (AESI) are defined in protocol Section 7.2.5 as hypersensitivity reactions, convulsions, *clostridioides difficile*-associated colitis or pseudomembranous colitis, hepatic enzyme increased, hyponatremia, renal failure, infusion site reactions, and thromboembolic events. These AESIs will be identified using the following narrow Standardized MedDRA Query (SMQ) or MedDRA PTs:

- Hypersensitivity reactions (Narrow SMQ code 20000214)
- Convulsions (Narrow SMQ code 20000079)
- *Clostridioides* (*Clostridium*) *difficile*-related AEs (Narrow SMQ code 20000080)
- Hepatic enzyme increased (PTs: Hepatic function abnormal, Alanine aminotransferase, Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Liver function test abnormal, Liver function test increased, Transaminases increased)
- Hyponatremia (PTs: Blood sodium decreased or Hyponatraemia)
- Acute renal failure (Narrow SMQ code 20000003)
- Extravasation events (injections, infusions and implants) (Broad SMQ code 20000136)
- Embolic and thrombotic events (Narrow SMQ code 20000081).

Adverse events of special interest will be summarized by SOC and PT.

9.2 Physical examination

Physical examination results for all patients will be presented in a listing.

9.3 Clinical laboratory evaluations

Local laboratory tests include hematology, blood chemistry, and urine analysis (dipstick) parameters in accordance with the protocol Schedule of Assessments and protocol Table 4.

Summary tables for laboratory parameters including actual values and change from baseline values will be presented for mandatory laboratory parameters with numeric values by visit.

Laboratory data will also be summarized using shift tables where appropriate. Each patient's continuous laboratory safety parameter values will be flagged as 'low', 'normal', or 'high' relative to the normal ranges of the laboratory. Each patient's categorical laboratory safety parameter values will be flagged as 'abnormal' or 'normal'. These categorical data will be summarized in shift tables comparing the minimum post-baseline value, maximum post-baseline value, and all other relevant post-baseline visits, with those at the baseline visit.

Laboratory data collected at unscheduled visits will be included in listings, and will contribute to tables of shifts from baseline and tables showing changes from baseline to

highest value and lowest value. Unscheduled laboratory results will not be windowed for the purposes of assigning a nominal visit.

All clinical laboratory parameters will be presented in a listing including normal ranges, and indicating if the value is out of range.

9.4 Vital signs

Summary tables of observed values and changes from baseline, as well as minimum and maximum post-baseline values, will be presented for vital-sign data, including weight (g), body temperature (°C), respiration rate (breaths/minute), pulse rate (bpm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and pulse oximetry (%), at each visit on a given timepoint, in the Safety population.

10 PHARMACOKINETICS

Plasma concentrations of ceftobiprole, ceftobiprole medocaril, and the open-ring metabolite will be reported at each time point specified in the protocol Schedule of Assessments.

Non-compartmental PK analysis and a population PK model will be developed and reported separately.

11 INTERIM ANALYSES

No interim analyses will be performed.

12 CHANGES IN THE PLANNED ANALYSIS

There are no changes between the protocol-defined statistical analyses and those presented in this SAP.

The definition of the CE population has been clarified in this SAP. Patients should have received at least 48 hours of study drug to be included in the CE.

13 APPENDICES

Appendix 1 Adverse event and prior/concomitant medication date imputations

Imputation rules for partial dates

Adverse event start date imputation

Parameter	Missing	Additional conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y is after Y of first dose	1 January
	D, M, Y	None – date completely missing	Date of first dose of study drug

D = day; M = month; Y = year; AE = adverse event.
Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.

Prior and concomitant medication start date imputation

Parameter	Missing	Imputation
Start date for medication	D	First day of the month under consideration
	D and M	1 January
	D, M, Y	1 January of the year of informed consent
Stop date for medication	D	Last day of the month under consideration
	D and M	31 December
	D, M, Y	31 December of the year of follow-up visit

D = day; M = month; Y = year.
Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.