Sponsor: Basilea Pharmaceutica International Ltd.

Study title: **A multicentre, randomized, investigator-blind, active-controlled study to evaluate the safety, tolerability, pharmacokinetics and efficacy of ceftobiprole versus intravenous standard-of-care cephalosporin treatment with or without vancomycin in paediatric patients aged from 3 months to less than 18 years with hospital-acquired pneumonia or community-acquired pneumonia requiring hospitalisation**

Study number: BPR-PIP-002

SAP version: Final 2.0 – 02 March 2020

Name/Title	Date	Signature
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LIST OF ABBREVIATIONS

AE	Adverse Event
CAP	Community-acquired Pneumonia
CE	Clinically Evaluable
CI	Confidence Interval
DSMB	Data and Safety Monitoring Board
EOT	End-of-treatment
HAP	Hospital-acquired Pneumonia
ITT	Intent-to-treat
IV	Intravenous
LFU	Last Follow-up
ME	Microbiologically Evaluable
mITT	Microbiological Intent-to-treat
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TOC	Test-of-cure
WBC	White Blood Cell Count

1 INTRODUCTION

This statistical analysis plan covers the detailed procedures for performing the statistical analyses and producing tables, listings and figures in the study described in Basilea Pharmaceutica International Ltd. (Basilea) Protocol BPR-PIP-002, version 3.0, dated 29 Nov 2018. The SAP version 1.0 has been amended to reflect the changes introduced in this latest version of the protocol.

1.1 Change from planned analysis

Considering the number of patients in the mITT and ME analysis populations, the microbiological data will only be listed.

2 STUDY OBJECTIVES, ENDPOINTS AND DESIGN

2.1 Study Objectives

2.1.1 Primary objective

The primary objective of this study is to characterise the safety profile of ceftobiprole in paediatric patients with hospital-acquired pneumonia (HAP) or community-acquired pneumonia (CAP) requiring hospitalisation and IV antibiotic therapy.

2.1.2 Secondary objectives

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

- To compare the clinical cure rate and microbiological eradication rate at the test-of-cure (TOC) visit between ceftobiprole and intravenous (IV) standard-of-care cephalosporin treatment (± vancomycin)
- To compare the clinical and microbiological relapse rates at the last follow-up (LFU) visit between ceftobiprole and IV standard-of-care cephalosporin treatment (± vancomycin)
- To characterise other efficacy measures of ceftobiprole (e.g., improvement in signs and symptoms of pneumonia, length of hospital stay)
- To assess the pharmacokinetics (PK) of ceftobiprole

2.2 Study Endpoints

2.2.1 Primary endpoint

The primary endpoint is:
Analysis of adverse events (AEs) assessed on each of the first 3 days of study-drug treatment, and at the end-of-treatment (EOT), TOC, and LFU visits (Safety population). Other timepoints may also be analysed.

2.2.2 Secondary endpoints

Secondary endpoints are:

2.2.2.1 Efficacy

- Comparison of clinical cure rates (intent-to-treat [ITT] and clinically evaluable [CE] populations) between ceftobiprole and the comparator at the TOC and LFU visits

- Comparison of microbiological eradication rates (microbiological ITT [mITT] and microbiologically evaluable [ME] populations) between ceftobiprole and the comparator at the TOC and LFU visits
- Comparison of clinical response at study Day 4 and at the EOT visit (ITT and CE populations)
- Comparison of the clinical and microbiological relapse rates at the LFU visit (ITT, CE, mITT, and ME populations)

2.2.2.2 Pharmacokinetics

- Descriptive analysis of ceftobiprole plasma concentration per time point, based on PK sampling in at least 15 patients in each of the two age categories of <6 years and ≥6 years (PK population).

2.3 Study Design

2.3.1 Study design and sample size

This is a randomized, investigator-blind, multiple-fixed dose, active-controlled multicentre study to be carried out in 138 paediatric patients (minimum of 125 evaluable patients) aged 3 months to <18 years, diagnosed with either HAP or CAP, requiring hospitalisation and treatment with systemic antibiotics.

Randomization will be stratified by four age groups (3 months to <2 years; 2 years to <6 years; 6 years to <12 years; 12 years to <18 years), and by diagnosis of HAP or CAP. Patients will be randomized 2:1 within each group to receive either ceftobiprole or the comparator standard-of-care IV cephalosporin antibiotic (ceftazidime with or without vancomycin for patients with HAP; ceftriaxone with or without vancomycin for patients with CAP). At least 50 patients are planned to be enrolled in each of the age categories <6 years and ≥6 years. There is no requirement for a minimum number of patients with each infection type (HAP or CAP)

2.3.2 Assessments

Table 1 presents a summary of the schedule of assessments that are to be performed from Screening to the final post-treatment visit.

Table 1: Schedule of Assessments

Assessment	**Screening**	**Active treatment**					**EOT***	**TOC**	**LFU****
Study Day	**Day −1 to 1**	**Day 1**	**Days 2–3**	**Day 4**	**Days 5–7**	**Day 8–14**		**7–14 days after EOT**	**28–35 days after EOT**
Written informed consent[1]	X								
Inclusion/exclusion criteria	X								
Medical history and demographics	X								
Prior medications[2]	X								
Pregnancy test[3]	X						X		
Physical examination	X			X			X		
Laboratory tests[4]	X			X			X	X	
Haptoglobin[5]	X			X			X		
Direct antiglobulin (Coombs) test[6]	X							X	
Vital signs and pulse oximetry[7]	X	X	X	X	X	X	X	X	

Pneumonia signs and symptoms	X	X	X	X	X	X	X	X	
Clinical pneumonia outcome assessment[8]				X			X		
Study medication		X	X	X	X	X			
Eligibility for IV to oral switch				X	X	X			
Concomitant medication[9]		X	X	X	X	X	X	X	X
Adverse events[10]		◄----- continuous from time of first study drug administration------►							
Imaging[11]	X								
Microbiological sampling[12]	X						X	X	X
Overall microbiological outcome								X	X
Overall clinical outcome[13]								X	X
PK sampling[14]			X						
Treatment/hospitalisation setting	X	X	X	X	X	X	X	X	X

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

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

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

[4] Laboratory tests include haematology, biochemistry, and urinalysis.

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

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

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

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

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

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

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

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

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

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

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

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

2.3.3 Interim analyses

An interim analysis of safety data will be performed by the Data Safety Monitoring Board (DSMB) after randomization of approximately 50 patients. The interim analysis as documented in the DSMB charter will focus on the safety of the subjects while the final analysis which is described in this document will include safety as well as efficacy endpoints.

In order to maintain blinding during the interim analyses, the following approaches will be adopted:

- Treatment groups will be identified by codes (A and B) in the interim analyses
- Blinded and unblinded statisticians/programmers will be assigned to the study
- Datasets that could lead to unblinding (EX, LB and PK) will only be available to the unblinded members of the team

The timing of data cut, analysis populations and other relevant information for the interim analysis can be found in the DSMB Charter for this study.

3 ANALYSIS POPULATIONS

3.1 Safety Population

All randomized patients who received at least one dose of study drug, analysed according to the first treatment actually received.

3.2 Intent-to-treat (ITT) Population

All randomized patients, analysed by treatment assigned. Should ITT and safety populations be identical, then all analyses would be performed for the ITT/safety population.

3.3 Clinically Evaluable (CE) Population

The CE population will be the subset of patients in the ITT population who have complied with important aspects of the study until TOC visit, i.e., with no major protocol deviations (e.g., had a valid clinical outcome assessment at TOC, no systemic non-study antibiotic therapy, etc…).

Major protocol deviations will be identified prior to the database lock and study unblinding.

3.4 Microbiological Intent-to-treat (mITT) Population

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

3.5 Microbiologically Evaluable (ME) Population

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

3.6 Pharmacokinetic (PK) Population

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

4 STATISTICAL CONSIDERATIONS AND ANALYSIS

4.1 General Considerations

Study results will be presented according to the following groups:

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

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

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

4.2 Derived Variables

The following derived variables will be applied throughout the study:

- Baseline is defined as the last available assessment prior to first dose intake (including unscheduled assessments).

- Last/Final for safety is the first available value after treatment or, if not available, then immediately before last treatment (but not before first treatment).

- Adverse event duration (in days) will be calculated as (the times will not be considered): Event end date - Event onset date + 1.

- The following algorithm will be used for the study day determination:

    - Day 1 = Day of first study drug administration. The day before day 1 is Day -1.
    - Prior to Day 1 the algorithm is (<visit/examination date> minus <date of first study drug administration >)
    - Day 1 and subsequent days = (<visit/examination date> minus <date of first study drug administration >) + 1.

- To reflect the birth date collection requirement for paediatric studies, age, expressed in years, will be calculated as follow:

    - if full date of birth collected: integer part of (consent date - date of birth)/365.25.
    - if only year of birth collected: consent year - year of birth

- Duration of exposure (in days) will be calculated as: Date of last study drug administration – Date of first study drug administration + 1.

4.3 Handling of Missing Data and/or Invalid Data and Outliers

When calculating the clinical outcome of therapy, subjects assessed as clinically unevaluable or withdrawn from the study before the TOC visit but after at least one treatment with study drug will be counted as clinical failure.

Incomplete/partial dates will be replaced by derived variables and imputed using the following rules:

- If the day of the month is missing it is imputed to be the 15th if not in the month of treatment. In case this leads to inconsistencies with other available patient's data, the imputation values will be handled on a case-by-case basis.
- If both the day and month are missing, they are imputed to be June 30 if not in year of treatment. In case this leads to inconsistencies with other available patient's data, the imputation values will be handled on a case-by-case basis.
- Missing years will be left as missing.
- Missing time will be replaced by '00:00' for start times and '23:59' for end times if time is required.
- Missing minutes will be replaced by '00' for start times and '59' for end times times if time is required.

4.4 Handling of Mis-stratification and Incorrect Treatment

In the case that a patient is stratified into the wrong stratum during randomization, the patient will be analysed based on the actual stratum depending on age and diagnosis. However, in the case that a patient is treated with a treatment other than the randomized treatment, the analyses will proceed as follows:

- For the Safety population, the patient will be analysed according to actual treatment received.
- For the ITT population, the patient will be analysed according to the treatment the patient was randomized to.
- For the CE and ME populations, the patient will be excluded from analysis.

4.5 Valid Pathogens

For assignment to the ME or the mITT population, the following pathogens will be considered:

- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Streptococcus species*
- *Pseudomonas aeruginosa*
- *Escherichia coli*
- *Moraxella catarrhalis*
- *Klebsiella species*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Burkholderia cepacia complex*
- *Bordetella pertussis*
- *Enterobacter species*
- *Citrobacter species*
- *Prevotella species*
- *Nocardia species*
- *Legionella species*
- *Serratia species*
- *Acinetobacter calcoaceticus*
- *Acinetobacter baumannii*

- *Stenotrophomonas maltophilia*

This list is not exhaustive and may be updated prior to database lock. A listing of subjects with any identified pathogens will be provided.

5 STATISTICAL PLAN AND METHODS

The statistical analysis will be performed using the software package SAS version 9.3 or higher (SAS Institute Inc., Cary, NC 27513, USA). All individual data as well as results of statistical analyses will be presented in individual patient data listings and statistical summary tables.

In general, continuous variables will be summarized using the following standard descriptive summary statistics: mean, standard deviation, median, minimum, maximum and number of observations. Categorical data will be described using frequency and percentage. Shift tables will be provided, where appropriate. One additional decimal point for mean, median, Q1, Q3 and two additional decimal points for SD will be used. Percentages will be rounded to one decimal place or more if most results are close to 0 or 100. Unscheduled assessments will only be listed and will not be included in the tables, unless otherwise specified. Any changes in the planned statistical methods will be documented in the clinical study report.

The following international dictionaries will be used for medical coding:

- Medical History events: MedDRA (version 20.1 or above)
- Medications: WHO Drug Dictionary Enhanced (March 2017 version or above)
- Adverse events: MedDRA (version 20.1 or above)
- Concomitant procedures: MedDRA (version 20.1 or above)

Data from all participating study centers will be combined for analysis.

5.1 Background Characteristics

5.1.1 Patient disposition

Enrollment and disposition data will be presented for each patient in data listings and summarized by frequency tables.

Inclusion and exclusion criteria deviations and patient enrollment eligibility will be presented by dose cohort and patient in data listings.

5.1.2 Protocol deviations

All protocol deviations reported by the clinical team will be tabulated and presented in a data listing sorted by center, category and patient.
Major protocol deviations are defined as those that could potentially bias either the efficacy or safety conclusions of the study. All other protocol deviations are defined as minor protocol deviations.
Protocol deviations will be reviewed prior to database lock to and classified as major or minor based on medical review.

5.2 Demographics and Other Baseline Characteristics

5.2.1 Demographics

Descriptive statistics of baseline data will be presented by treatment group. The following baseline demographic data will be presented:

- Age [years] at consent
    - Continuous summary
- Sex
    - Categorical summary (Male, Female)
- Race

- Categorical summary (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)

- Height [cm]
  - Continuous summary
- Weight [kg]
  - Continuous summary

5.2.2 Medical history

Medical history of other diseases will be summarized in tables by treatment groups, SOC, and PT, including number of subjects and percentage relative to the numbers of subjects in the corresponding study groups.

5.3 Prior and Concomitant Medications

Data concerning concomitant medications and procedures will be collected throughout the study. These data will be obtained at scheduled or unscheduled study visits, based on information provided by the subject's parent or legal guardian.

The coding of medications will be performed using the WHODRUG enhanced dictionary and partial start and/or end dates will be imputed as described in section 4.3.

Medications will be classified based on the observed or imputed start dates into:

- A medication is classified as prior if it started and stopped before the reference start date of the subject.
- A medication is classified as concomitant medication if it started on or after the reference start date of the subject.
- A medication is classified as ongoing if it started before the reference start date of the subject and is still ongoing after the reference start date.

Prior medications, concomitant and ongoing medications will be presented in a listing.

Concomitant and ongoing medications will be summarized in tables by treatment groups, Anatomical Therapeutic Chemical (ATC) level 4 code, and Preferred Term (PT), including number of subjects and percentage relative to the numbers of subjects in the corresponding study groups.

5.4 Treatment Compliance and Exposure

The overall exposure to study drug adjusted by baseline weight will be summarized by treatment group, age group and infection type. The total dose taken at specific time points and at the end of the study will be presented.

Treatment compliance per administration will be computed as:

Compliance [%] = (actual dose (mg) / planned dose (mg))*100.

Overall treatment compliance for intravenous treatment for each subject will be computed as the total dose administered (mg) / total planned dose (mg)) *100 and summarized.

In addition, the duration of intravenous and oral treatments (for subjects who switched to oral treatment) as well as the time-to-switch will be summarized.

5.5 Primary and secondary endpoint analysis

5.5.1 Primary endpoint analysis

The primary endpoint of this study is the analysis of adverse events assessed on each of the first 3 days of study-drug treatment, and at the end-of-treatment, test-of-cure and last follow-up visits. A summary table will be presented for all adverse events by treatment group, age group and infection type. This will be done for the Safety population.

Adverse events will be presented cumulatively. In addition, a summary of all adverse events experienced while patients are on IV therapy irrespective of when they switch treatment will be presented.

5.5.2 Secondary endpoint analysis

For the secondary endpoints, some efficacy analysis will be computed based on some pre-planned efficacy evaluations which can be found in the study protocol. No formal hypothesis tests are planned.

5.5.2.1 Clinical cure rate

Clinical cure is defined as signs and symptoms of pneumonia normalized or improved to an extent that further antibiotic therapy is not necessary, with lack of progression of chest X-ray abnormalities post-baseline if these are available. As the protocol does not require repeat chest X-rays after screening unless clinically indicated, patients with clinical improvement without a repeat chest X-ray would be considered to have lack of progression of X-ray abnormalities. This endpoint will use the difference of proportions to assess the difference in the clinical cure rate between the treatment groups at the TOC visit. The 95% confidence interval using the Exact method will also be computed. This will be done for both the ITT and the CE populations. All analysis will be done by infection type and overall.

5.5.2.2 Clinical relapse

The clinical relapse rate and presumed relapse rate (ITT and CE) between treatment groups at the LFU visit will also be compared using difference of proportions. The 95% confidence interval will be computed using the Exact method.

5.5.2.3 Other efficacy analysis

Descriptive statistics will be presented for changes from baseline in signs and symptoms and in overall clinical status. Duration of hospitalisation, defined as the time from start of study drug therapy to discharge, will also be analysed by descriptive statistics and by a time-to-event analysis.

Re-hospitalizations will not be considered in the calculation of duration of hospitalization.

The other efficacy data collected e.g. microbiological assessments alongside any valid pathogens and resistance will be listed.

5.5.2.4 Pharmacokinetic analysis

Plasma concentrations of ceftobiprole, ceftobiprole medocaril, and open-ring metabolite will be summarized by descriptive statistics. This analysis will be done by age group (3 months to <2 years, 2 years to <6 years, 6 years to <12 years, 12 years to <18 years).

Further pharmacokinetic data analyses will be described and summarized separately.

5.6 Safety Analysis

Definitions of adverse events (AEs) and serious adverse events (SAEs) as well as information on reporting procedures for AEs/SAEs are provided in the clinical trial protocol. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1 or above) and partial start and/or end dates will be imputed as described in section 4.3.

Frequency tables summarizing the incidence and observed number of treatment-emergent adverse events by treatment and by System Organ Class and Preferred Term will be prepared with 3 levels of detail:

- All adverse events
- Adverse events by severity (mild/moderate/severe)
- Adverse events by relationship to study drug (not related/unlikely/possible/ probable)

Summary tables for all adverse events and for adverse events by severity will be split by treatment group, age groups, infection type and overall.

5.7 Clinical Laboratory Evaluations

The laboratory parameters collected per protocol will be described using summary statistics and shift tables. Summary statistics will be presented for absolute values and absolute change from baseline. Where reference indicators (low/high, negative/positive or normal/abnormal) are present however, shift tables will, in addition be presented to show shifts from baseline values at the different time points. Adverse changes from baseline to first post-dose results will also be summarized.

5.8 Vital Signs

The actual and change from baseline values of the following vital signs will be summarized using descriptive statistics. In addition, change from baseline values for patients with values outside marked reference range will also be summarized.

- Systolic blood pressure
- Diastolic blood pressure
- Pulse rate
- Temperature
- Respiration rate

5.9 Physical Examination

Abnormal results in physical examinations will be summarized by visit while all data will be listed.

6 REFERENCES

- EMEA. CPMP/ICH/363/96: Note for Guidance on Statistical Principles for Clinical Trials - ICH Topic E9. London: EMEA; 1998.
- Integrated Addendum to ICH E6(R1), GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 9 November 2016.