| Clinical Study Protocol | |
|---|---|
| Drug Substance | Ceftaroline fosamil |
| United States (US) Investigational New Drug (IND) Number: | 71,371 |
| European Clinical Trials Database (EudraCT) Number: | 2014-003243-34 |
| Pfizer Study Code | C2661002 |
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| Version | 5.0 |
| Phase | 2 |
| Date | 25 May 2017 |

# Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline in Neonates and Young Infants with Late-Onset Sepsis

**Sponsor:** *Pfizer Inc., 235 East 42nd Street, New York, NY 10017, USA (as of Version 5.0)*

**Prior Sponsor:** *AstraZeneca AB, 151 85 Södertälje, Sweden*

[redacted]

[redacted]

## VERSION HISTORY

| Version 5.0, 25 May 2017 |
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| The previous version of the protocol (Edition 4, dated 25 August 2015) has been revised to reflect change in Sponsorship to Pfizer Inc and to include the latest protocol template language of the current Sponsor, Pfizer. The visit window for the Safety Follow Up (SFU) assessment was changed to 28 to 35 days to be consistent with Pfizer's requirement to follow safety for a minimum of 28 days after the last dose of study therapy. In addition, minor text changes were made to improve protocol clarity. |

| Version 4, 25 August 2016 |
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| The previous version of the protocol (Edition 3, dated 16 December 2015) has been transferred to the latest AstraZeneca designated template (Protocol Template Version 17.0). In addition, the following changes were incorporated into Version 4 of the protocol:<br>• Date of pediatric approval in the US (May 2016) and EU (June 2016) was added.<br>• Inclusion criterion 5 was revised so that patients must meet at least 1 of the listed laboratory criteria, rather than 2 of the criteria.<br>• Following a request from the Italian Ministry of Health, a justification was provided for the dose increase to 6 mg/kg that was described in Edition 3 of the protocol.<br>• Clarification was added to the effect that the individual dose of Ceftaroline fosamil should be calculated based on the patient's first weight of the day.<br>Note: previous versions of the protocol were numbered "Edition 1", "Edition 2", etc, but "Edition" has now been replaced with "Version". |

| Edition 3, 16 December 2015 |
|---|
| • An AstraZeneca Research and Development site representative was added as a signatory to the revised protocol.<br>• Clarification was provided for when ampicillin administration is mandatory.<br>• The dose of ceftaroline fosamil to be given was increased to 6 mg/kg.<br>• The estimated date for last patient completed and study end were updated to align with the Pediatric Investigation Plan for ceftaroline fosamil.<br>• Minor wording changes were added to the text as clarifications.<br>Note: in addition to the changes listed above, minor formatting/style changes were made. |

| **Edition 2, 23 April 2015** |
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| 1. The definition of preterm neonate was revised in order to align with the World Health Organization definition of preterm neonates used world-wide. The age requirement for Cohort 2 (term neonates) was therefore revised from gestational age ≥38 weeks to gestational age ≥37 weeks. The age requirement for Cohort 3 (preterm neonates) was revised from gestational age ≥34 to <38 weeks to gestational age ≥34 to <37 weeks.<br>2. The discrepancy between units and values for white blood cell and platelet counts in the inclusion criteria was corrected.<br>3. The definition of Study Day was clarified – Study Days were to be calculated starting from the onset of the first dose of study therapy, in 24-hour increments.<br>In addition, some minor typographic errors were corrected. |

| **Edition 1, 18 November 2013** |
|---|
| Initial creation |

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional boards (IRBs)/ethics committees (ECs).

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to the Sponsor and opportunity to object.

The clinical study protocol is publicly registered and the results are disclosed and/or published according to the Sponsor publication policy and in compliance with prevailing laws and regulations.

## PROTOCOL SYNOPSIS

# Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline in Neonates and Young Infants with Late-Onset Sepsis

### International Co-ordinating Investigator

The name and contact details of the International Co-ordinating Investigator will be communicated by the Sponsor or Sponsor representative to all study centres and any applicable regulatory authorities via a certified letter.

### Study site(s) and number of patients planned

The study will be conducted in approximately 30 centres worldwide. At least 24 patients evaluable for safety will be enrolled and treated within the following age cohorts:

- Cohort 1: young infants aged >28 days to <60 days (n=8)
- Cohort 2: term neonates (defined as gestational age ≥37 weeks) aged 7 to ≤28 days (n=8)
- Cohort 3: preterm neonates (defined as gestational age ≥34 to <37 weeks) aged 7 to ≤28 days (n=8).

| Study period | |
|---|---|
| Estimated date of first patient enrolled | Q1 2015 |
| Estimated date of last patient completed | December 2017 |

### Study design

This is a multicentre, multinational, open-label, single treatment arm study of intravenous (IV) ceftaroline fosamil and ampicillin, plus an optional aminoglycoside of choice, in hospitalized neonates and young infants aged 7 to <60 days with late-onset sepsis (LOS).

Baseline assessments for study eligibility will occur within 36 hours before administration of the first dose of study therapy. Study Day 1 is defined as the 24-hour period starting at the onset of the first administration of study therapy. Thereafter, subsequent Study Days are to follow the same pattern.

Safety assessments will occur throughout the study. Clinical outcome evaluations will occur at End-of-Therapy (EOT; within 24 hours after completion of last infusion) and Test-of-Cure (TOC; 8 to 15 days after the last dose of study therapy).

**Objectives**

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To evaluate the safety and tolerability of ceftaroline for the treatment of LOS in neonates and young infants aged 7 to <60 days | Safety assessments will include adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs. |

| **Secondary Objective:** | **Outcome Measure :** |
|---|---|
| To evaluate the pharmacokinetic profile of ceftaroline in neonates and young infants aged 7 to <60 days with LOS | Concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma (and if available, concentrations of ceftaroline and ceftaroline M-1 in cerebrospinal fluid [CSF]) |
| To evaluate the efficacy of ceftaroline for the treatment of LOS in neonates and young infants aged 7 to <60 days | Efficacy outcome measures will include clinical outcome at EOT and TOC in the Modified Intent-to-Treat (MITT) Analysis Set. |

**Target patient population**

Male or female patients, gestational age ≥34 weeks, and chronological age 7 to <60 days with a diagnosis of sepsis within 36 hours before enrolment, defined as the presence of at least 2 clinical criteria and at least 1 laboratory criterion in the presence of or as a result of suspected or proven bacterial infection that requires IV antibiotic therapy.

**Duration of treatment**

Patient participation will require up to 49 days. The total duration of study therapy is 48 hours (minimum) to 14 days (maximum). Hospitalization is required while on IV study therapy. Baseline assessments for study eligibility will occur within 36 hours before the first dose of study therapy. The Safety Follow-up (SFU) assessments will occur 28 to 35 days after the last dose of study therapy.

**Investigational product, dosage and mode of administration**

Ceftaroline fosamil will be given at a dose of 6 mg/kg IV over 60 (± 10) minutes every 8 hours (q8h) (± 1 hour). IV ampicillin and optional aminoglycoside will be given as per standard of care. If the presence of an organism that requires treatment with ampicillin cannot be excluded, then the use of IV ampicillin for the first 48 hours is mandatory. If the results of additional microbiology, polymerase chain reaction (PCR) or other investigations indicate that ampicillin during the first 48 hours of treatment is not required, then its use is at the discretion of the investigator.

**Statistical methods**

Descriptive statistics (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 summarized overall and by age cohort. Listings of individual patients' data will also be produced.

The primary objective of this study is to evaluate the safety and tolerability of ceftaroline in neonates and young infants with LOS and the study is not powered for formal statistical inference. The Safety Analysis Set will include all patients who received any amount of ceftaroline fosamil. Safety parameters include AEs, SAEs, deaths, clinical laboratory parameters, and vital signs. For each safety parameter, the last assessment made before the first dose of study therapy will be used as the baseline for all analyses. The incidence of adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs will be summarized overall and within each age cohort, by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), by relationship to the study therapy, and by severity.

Efficacy outcomes will be summarized descriptively using the modified Intent-to-treat (MITT) Analysis Set, which will include all patients who receive any amount of ceftaroline fosamil and who meet minimal disease criteria of LOS. An assessment of clinical outcome will be made by the investigator at EOT. Possible outcomes are clinical cure, clinical failure or indeterminate. A favourable clinical outcome is clinical cure. An outcome of clinical failure at EOT will be carried forward to TOC. A further assessment of clinical outcome will be made at TOC.

Per-patient microbiological response at TOC will be determined programmatically based on individual outcomes for each baseline pathogen. In order for a patient to have a favourable microbiological response, the outcome for each baseline pathogen must be favourable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavourable (persistence or presumed persistence), the patient will be considered to have an unfavourable microbiological response.

Summaries of demographics and other baseline characteristics will be provided. The incidence of AEs, SAEs, deaths, and discontinuations due to AEs will be summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities, by relationship to study therapy, and by severity. Descriptive statistics of observed results and the change from baseline to selected postbaseline time points will be presented for clinical laboratory results and vital signs. The incidence of selected potentially clinically significant laboratory results will be summarized.

The pharmacokinetic (PK) Analysis Set will include all patients who receive a known amount of ceftaroline fosamil and who have had at least 1 PK sample collected. The PK data acquisition and analysis strategy in this study entails the use of a sparse PK sampling schedule, conducted only at selected investigational centres. Plasma concentrations of

ceftaroline fosamil, ceftaroline and ceftaroline M-1, and cerebrospinal fluid (CSF) concentrations of ceftaroline and ceftaroline M-1 will be listed by age cohort. Ceftaroline plasma concentration data, along with other information including demographic data, will be combined with appropriate data from other clinical studies and analysed using a population PK approach and reported separately.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| ABSSSI | Acute bacterial skin and skin structure infections |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| $AUC_{0-24h}$ | Area under the curve from 0 to 24 hours |
| BE | Base excess |
| CA | Competent Authority |
| CABP | Community acquired bacterial pneumonia |
| CAP | Community-acquired pneumonia |
| CBC | Complete blood count |
| CRF | Case report form |
| $C_{max}$ | Maximum concentration |
| CNS | Central nervous system |
| CRF | Case Report Form (electronic/paper) |
| CRP | C-reactive protein |
| CRS | Catheter-related sepsis |
| CSA | Clinical Study Agreement |
| CSF | Cerebrospinal fluid |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| CXR | Chest radiograph |
| DILI | Drug-induced liver injury |
| DSMB | Data and Safety Monitoring Board |
| EDC | Electronic data capture |
| EOT | End-of-Therapy |
| EudraCT | European Clinical Trials Database |
| FDA | Food and Drug Administration |

| Abbreviation or special term | Explanation |
|---|---|
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| International Co-ordinating investigator | If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally |
| IP | Investigational product |
| IRB | Institutional Review Board |
| ITT | Intent-to-treat |
| IV | Intravenous |
| IXRS | Interactive voice/web response system |
| LOS | Late-onset sepsis |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIC | Minimum inhibitory concentration |
| MITT | Modified intent-to-treat (MITT) |
| MRI | Magnetic resonance imaging |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| NEC | Necrotizing enterocolitis |
| PCR | Polymerase chain reaction |
| PCS | Potentially clinically significant |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PTA | Probability of target attainment |
| q8h | Every 8 hours |
| q12h | Every 12 hours |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |

| Abbreviation or special term | Explanation |
|---|---|
| SFU | Safety follow-up |
| SPC | Summary of product characteristics |
| Tbili | Total bilirubin |
| TOC | Test-of-Cure |
| ULN | Upper limit of normal |
| US | United States |

# 1. INTRODUCTION

## 1.1. Background and rationale for conducting this study

Ceftaroline is a β-lactam antibiotic of the cephalosporin class with broad-spectrum activity against gram-positive bacteria including methicillin resistant Staphylococcus aureus (MRSA) and penicillin-resistant S. pneumonia (PRSP), as well as against common gram-negative bacteria. Ceftaroline inhibits bacterial cell wall biosynthesis by binding to 1 or more penicillin-binding proteins, which inhibits their function and causes the bacteria to die. Ceftaroline exhibits unique properties that distinguish it from other β-lactams due to its high affinity for PBP2a in MRSA, and PBP2x in PRSP that contribute to its potent antibacterial activity against these organisms.

Teflaro® (ceftaroline fosamil, the prodrug of ceftaroline) is indicated in adult and pediatric patients 2 months of age and older for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and for the treatment of community-acquired bacterial pneumonia (CABP). Teflaro was approved in the US for ABSSSI and CABP in adults in October 2010. Pediatric approval in the US was May 2016. In August 2012, it was approved as Zinforo™ for use in adults for the treatment of complicated skin and soft tissue infection and community-acquired pneumonia (CAP) in the European Union and Chile. Pediatric approval in the European Union was June 2016. Since 2012, Zinforo™ has been approved in over 50 countries, including Russia, Australia, Malaysia, and Singapore, and approval is being sought in additional countries. Refer to the current ceftaroline fosamil Investigator's Brochure (IB) and ceftaroline fosamil product information[18,19] for summaries of the nonclinical, microbiology, pharmacology, and clinical studies.

A pediatric development program to evaluate the use of ceftaroline fosamil in children under 18 years old is currently underway. Two Phase I studies designed to assess the safety, tolerability, and pharmacokinetics (PK) of ceftaroline fosamil in children have been completed (Study P903-15 in adolescent patients aged 12 to 17 years and Study P903-21 in children aged from birth to <12 years). The program includes three completed studies in patients from 2 months to <18 years of age: 2 Phase 2/3 studies (Study P903-23 in ABSSSI and Study P903-31 in CABP requiring hospitalization) and a Phase 4 study (Study P903-24 in complicated CABP).

Late-onset sepsis (LOS), or sepsis neonatorum, is a severe infectious disease, one of the main causes of mortality and morbidity among neonates and young infants around the world, and has different epidemiology, microbiology, and pathophysiology than other age populations.[1,8]

The purpose of this study is to assess the safety, tolerability, PK, and efficacy of ceftaroline fosamil and ampicillin, plus an optional aminoglycoside of choice, in neonates and young infants with LOS.

### 1.2. Rationale for study design, doses and control groups

This open-label, multicentre, multinational, single treatment arm study will evaluate the safety, tolerability, PK, and efficacy of ceftaroline in the target population, neonates and young infants with LOS. Pediatric patients (7 to <60 days) with suspected or confirmed LOS will be enrolled in this study.

The aetiology of LOS is nosocomial or community acquired. Ceftaroline has activity against common gram-positive pathogens, including MRSA, and gram-negative pathogens including Enterobacteriaceae (with the exception of those producing extended-spectrum β-lactamase), which makes it appropriate for use in community-acquired and nosocomial infections.[5,14,18]

Immediate administration of antibiotic therapy with broad-spectrum activity is critical in patients with LOS. The purpose of therapy is to prevent morbidity and decrease mortality which is likely to happen without therapy or with inadequate therapy. Starting the appropriate antibacterial drug without delay, while awaiting culture results, decreases mortality rate dramatically.[4,10] As therapy must be prescribed as soon as possible, the choice of drugs should be made empirically based on epidemiology and possible aetiology agent. The priority should be given to bactericidal drugs with broad-spectrum coverage of gram-positive and gram negative microorganisms.

Ceftaroline, with its broad-spectrum activity has the potential to provide a valuable therapeutic option in the treatment of LOS. Ceftaroline was well tolerated in adult and pediatric clinical trials and has a safety profile consistent with available marketed cephalosporins, a class of antibiotics with a long history of clinical use.

The combination of ampicillin and an optional aminoglycoside of choice was chosen as the recommended empirical therapy because of its ability to achieve maximum coverage of gram-positive and gram-negative pathogens of LOS and as an effective standard of care antibiotic therapy for this indication, which is accepted in clinical practice worldwide.[2,9,11,15,16,17]

The dosing regimen for ceftaroline (6mg/kg q8h as a 1-hour infusion) was chosen based on a population PK model updated with PK data from three multiple dose safety and efficacy studies in children from 2 months to <18 years (Studies P903-23, P903-31 and P903-24).[13] These data have been used in conjunction with adult patient and healthy volunteer data and data from single dose ceftaroline PK studies conducted in children from neonates to <18 years. The ceftaroline population PK model incorporates allometric scaling for body weight and maturation of renal function. This model was used in Monte Carlo simulations to choose and justify the dose regimens for children from 2 months to 18 years, now included on the European Summary of Product Characteristics (SmPC) and US Food and Drug Administration (FDA) label. The same model has been used to predict doses for children <2 months, including pre-term neonates (with a post-menstrual age of 28 to 41 weeks). Post-menstrual age is defined as gestational age plus chronological age. Various dosing regimens simulated using body weights for each simulated patient were predicted based on

age in accordance with either CDC growth charts[7] for neonates that were born to term or in accordance with intrauterine growth curves[12] for preterm and to-term neonates (gestational age 32-40 weeks). One hundred simulations were performed for each dose with 600 (300 male and 300 female) patients from each age group. The age groups were categorised as follows: 28 to <30, 30 to <32, 32 to <34, 34 to <36, 36 to <38, 38 to <40 post-menstrual weeks, 0 to <1, 1 to <2, 2 to <6, 6 to <12, 12 to <18, 18 to <24 months.

Using this model, several dose regimens have been assessed and a dose of 6mg/kg ceftaroline fosamil q8h as a 1-hour infusion is predicted to achieve >90% probability of target attainment (PTA) for minimum inhibitory concentrations (MICs) ≤2mg/L. Predicted ceftaroline exposures (based on steady-state maximum concentration [$C_{max}$] and area under the curve from 0 to 24 hours [$AUC_{0-24h}$]) in pediatric patients younger than 2 months old and of gestational age 32-48 weeks dosed with 6 mg/kg q8h as a 1-hour infusion do not appreciably exceed ceftaroline exposures in adults dosed with the currently approved ceftaroline fosamil regimen of 600 mg every 12 hours (q12h). The median steady-state ceftaroline $C_{max}$ values in pediatric patients in this age range dosed with the proposed regimen are predicted to be less than the median $C_{max}$ value in adults dosed with 600 mg q12h. Median steady-state ceftaroline $AUC_{0-24h}$ values in pediatric patients younger than 2 months old and of gestational age 32-48 weeks dosed with the proposed regimen are predicted to be no more than 17% higher than the median adult value.

Based on these findings, the updated model has been used to optimise the dose (6mg/kg q8h as a 1-hour infusion).

### 1.3. Benefit/risk and ethical assessment

Patients enrolled into this clinical study will have LOS of sufficient severity to require hospitalization and treatment with IV antibiotics. The potential benefit to patients participating in this study is that they will receive effective antibiotic therapy for their infection. The potential benefit of this study, in general, is the identification of a new addition to the available antibiotic therapy that is a safe and effective treatment for LOS, in the face of the changing pattern of antibiotic resistance.

It is possible that ceftaroline fosamil and ampicillin will not prove to be a sufficiently effective treatment for LOS. This risk is mitigated by the possible option of adding an aminoglycoside, by close monitoring of study patients, and by management with appropriate therapies as determined by the investigator providing treatment.

The risk considerations for this study encompass the known and potential risks for ceftaroline fosamil, as well as those risks associated with other treatments that may be administered as described in this protocol (ampicillin and optional aminoglycoside). As the risks for these marketed products are widely available in their respective prescribing information, these risks will not be discussed within this section.

The risks for use of ceftaroline fosamil in children <2 months of age have not been fully elucidated; however it is assumed that known or potential risks for ceftaroline fosamil should include those identified from adult use and in clinical studies in adults and in children and adolescents. Additional risk information for ceftaroline fosamil is located in the Investigator's Brochure.

The full risk profile for ceftaroline fosamil is described in the prescribing information for the product. Important risks as laid out in the warnings and precautions in product labelling for ceftaroline fosamil include:

- Hypersensitivity reactions: though patients with hypersensitivity reactions to β lactam antibiotics are excluded from the trial, first-time episodes of such reactions could occur.
- Antibiotic-associated diarrhoea: Clostridium difficile-associated diarrhoea has been reported for nearly all systemic antibacterial agents, including ceftaroline fosamil, and may range in severity from mild diarrhoea to fatal colitis.
- Direct Coombs' Test Seroconversion: seroconversion from a negative to a positive test result occurred in more patients receiving ceftaroline fosamil than comparator drugs in pooled data from 4 Phase III clinical trials. If anaemia develops during or after treatment with ceftaroline fosamil, drug-induced haemolytic anaemia should be considered.
- Development of Drug-Resistant Bacteria: prescribing ceftaroline fosamil in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- Adverse Reactions: in the four pooled Phase III clinical trials, SAEs occurred in 98/1300 (7.5%) of patients receiving ceftaroline fosamil and 100/1297 (7.7%) of patients receiving comparator drugs. Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving ceftaroline fosamil and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the ceftaroline fosamil group and 0.5% in the comparator group.
- No adverse reactions occurred in greater than 5% of patients receiving ceftaroline fosamil. The most common adverse reactions occurring in >2% of patients receiving ceftaroline fosamil in the pooled Phase 3 clinical trials were diarrhea, nausea, and rash.

No clinical drug-drug interaction studies have been conducted with ceftaroline fosamil. There is minimal potential for drug-drug interactions between ceftaroline fosamil and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow.

Safety and effectiveness in pediatric patients <2 months of age have not been established.

Dosage adjustment is required in patients with moderate or severe renal impairment and in patients with end-stage renal disease (CrCl <15 mL/min).

The PK of ceftaroline in patients with hepatic impairment has not been established.

### 1.4. Study Design

This will be an open-label, single arm study with no randomization. The study will be conducted in approximately 30 centres worldwide. At least 24 patients with LOS will be enrolled and treated within three age cohorts of 8 patients: young infants aged >28 days to <60 days; term neonates aged 7 to ≤28 days; and preterm neonates aged 7 to ≤28 days.

Study therapy consists of standard of care ampicillin plus an optional aminoglycoside of choice, with the addition of intravenous (IV) ceftaroline fosamil, and will be given to all patients. If the presence of an organism that requires treatment with ampicillin cannot be excluded, then the use of IV ampicillin for the first 48 hours is mandatory. If the results of additional microbiology, polymerase chain reaction (PCR) or other investigations indicate that ampicillin during the first 48 hours of treatment is not required, then its use is at the discretion of the investigator.

Ceftaroline fosamil will be given at a dose of 6 mg/kg IV over 60 (± 10) minutes q8h (± 1 hour).

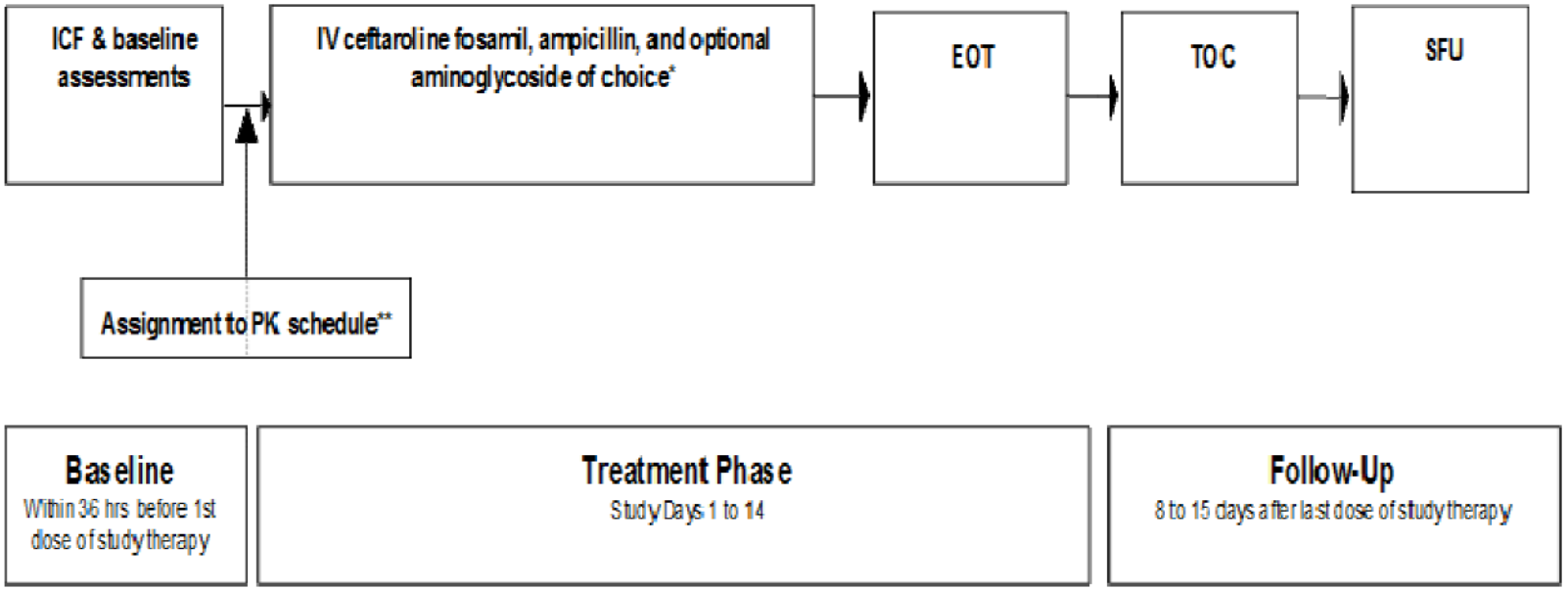
Patient participation will require up to 49 days. The total duration of study therapy is 48 hours (minimum) to 14 days (maximum). Hospitalization is required during IV study therapy. Baseline assessments for study eligibility will occur within 36 hours before the first dose of study therapy. The Safety Follow-up (SFU) assessments will occur 28 to 35 days after the last dose of study therapy.

Safety assessments will be done throughout the study. Between Day 2 and Day 14, 2 blood samples will be collected for PK analysis. The efficacy of ceftaroline will be evaluated based on the clinical outcome (clinical cure, clinical failure or intermediate) at end of therapy (EOT) and test-of-cure (TOC) assessment.

An external Data and Safety Monitoring Board (DSMB) will review data on a regular basis to assess the safety of all patients enrolled in this and other ongoing pediatric studies (Section 6.5.1).

The study design is described in the Study Diagram (Figure 1).

**Figure 1 Study Diagram**




Abbreviations: EOT = end of therapy; ICF = informed consent form; IV = intravenous; PK = pharmacokinetic; SFU = safety follow-up; TOC = test of cure

An external Data and Safety Monitoring Board (DSMB) will be established to review safety data from this study and other ongoing pediatric studies of ceftaroline fosamil on a regular basis to ensure safety of all subjects enrolled

* IV ampicillin and optional aminoglycoside will be given as per standard of care. If the presence of an organism that requires treatment with ampicillin cannot be excluded, then the use of IV ampicillin for the first 48 hours is mandatory. If the result of additional microbiology, polymerase chain reaction or other investigations, indicate that ampicillin during the first 48 hours of treatment is not required, then its use is at the discretion of the investigator

** Patients will be randomly assigned to PK schedule using IXRS

# 2. STUDY OBJECTIVES

## 2.1. Primary objective

| Primary Objective: | Outcome Measure: |
|---|---|
| To evaluate the safety and tolerability of ceftaroline for the treatment of LOS in neonates and young infants aged 7 to <60 days | Safety evaluations will be conducted in the Safety Analysis Set and assessments will include AEs, SAEs, deaths, and discontinuations due to AEs. |

## 2.2. Secondary objectives

| Secondary Objective: | Outcome Measure : |
|---|---|
| To evaluate the PK profile of ceftaroline in neonates and young infants aged 7 to <60 days with LOS | Concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma (and if available, concentrations of ceftaroline and ceftaroline M-1 in cerebrospinal fluid [CSF]) |
| Evaluate the efficacy of ceftaroline for the treatment of LOS in neonates and young infants aged 7 to <60 days | Efficacy outcome measures will include clinical outcome at EOT and TOC in the Modified Intent-to-Treat (MITT) Analysis Set. |

## 2.3. Safety objectives

Safety is the primary objective.

## 2.4. Exploratory objectives (not applicable)

# 3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by the investigator or appropriate member his/her site study team before subjects are included in the study. Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

## 3.1. Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Informed consent in writing from parent(s) or other legally-acceptable representative(s)

2. Male or female, gestational age ≥34 weeks, and chronological age 7 to <60 days at the time of screening

3. Diagnosis of sepsis within 36 hours before enrolment, defined as the presence of at least 2 clinical criteria and at least 1 laboratory criterion in the presence of or as a result of suspected or proven bacterial infection that requires IV antibiotic therapy.

4. Patients must meet at least 2 of the following clinical criteria:

   a. Hypothermia (<36°C) OR fever (>38.5°C)

   b. Bradycardia OR tachycardia OR rhythm instability

   c. Urine output 0.5 to 1 mL/kg/h OR hypotension OR mottled skin OR impaired peripheral perfusion

   d. Petechial rash OR sclerema neonatorum

   e. New onset or worsening of apnoea episodes OR tachypnoea episodes OR increased oxygen requirements OR requirement for ventilation support

   f. Feeding intolerance OR poor sucking OR abdominal distension

   g. Irritability

   h. Lethargy

   i. Hypotonia.

5. Patients must meet at least 1 of the following laboratory criteria:

   a. White blood cell count $\leq 4.0 \times 10^9$/L OR $\geq 20.0 \times 10^9$/L

   b. Immature to total neutrophil ratio >0.2

   c. Platelet count $\leq 100 \times 10^9$/L

   d. C-reactive protein (CRP) >15 mg/L OR procalcitonin ≥2 ng/mL

   e. Hyperglycaemia OR Hypoglycaemia

   f. Metabolic acidosis.

**3.2. Exclusion criteria**

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Documented history of any hypersensitivity or allergic reaction to any β-lactam antibiotic or aminoglycoside

2. At study entry, has confirmed infection with a pathogen known to be resistant to the combination of ceftaroline fosamil, ampicillin, and the optional aminoglycoside of choice OR confirmed viral, fungal, or parasitic pathogen as the sole cause of infection

3. Refractory septic shock within 24 hours before enrolment that does not resolve after 60 minutes of vasopressor therapy

4. Moderate or severe renal impairment defined as serum creatinine ≥2 times the upper limit of normal (× ULN) for age OR urine output <0.5 mL/kg/h (measured over at least 8 hours) OR requirement for dialysis

5. Evidence of progressively fatal underlying disease, or life expectancy of ≤60 days

6. Documented history of seizure

7. Requiring or currently taking antiretroviral therapy for human immunodeficiency virus (HIV) or a child from an HIV positive mother

8. Proven or suspected central nervous system (CNS) infection (eg, meningitis, brain abscess, subdural abscess), osteomyelitis, endocarditis, or necrotizing enterocolitis (NEC)

9. Any condition (eg, cystic fibrosis, urea cycle disorders), antepartum/peripartum factors, or procedures that would, in the opinion of the investigator, make the patient unsuitable for the study, place a patient at risk, or compromise the quality of data

10. Patient's parent(s) or legally-acceptable representative(s) involvement in the planning and/or conduct of the study (applies to both Sponsor staff and/or staff at the study site). Concurrent participation in another clinical study with an investigational product (IP), previous enrolment/participation in this study, or participation in another study of ceftaroline fosamil within 14 days before the intended start of the first dose of study therapy.

For procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

### 3.3. Patient enrolment

This is a non-randomized open-label study. Patients will be enrolled if they meet all the inclusion criteria, including informed consent in writing from parent(s) or other legally-acceptable representative(s), and none of the exclusion criteria. Patients will be stratified by age cohort as described in Section 3.5.1. Patients will be randomly assigned in the PK portion of the study to PK Schedule 1 or 2 (Section 3.5.2).

The investigator(s) will be responsible for patient management. Assessments and procedures should be conducted as noted in Section 4. The Pharmacist or designee will prepare study therapy infusions and manage dose adjustments, as applicable.

Patients who are withdrawn from study before receiving any amount of study therapy will be replaced in order to enrol a total of 24 treated patients for safety evaluations.

### 3.4. Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment.

Where a patient does not meet all the eligibility criteria but is incorrectly started on treatment, the investigator should inform the Sponsor study physician/designee immediately, and a discussion should occur between the Sponsor study physician/designee and the investigator regarding whether to continue or discontinue the patient from treatment. The Sponsor study physician/designee must ensure all decisions are appropriately documented.

### 3.5. Methods for assigning treatment groups

#### 3.5.1. Stratification by age and cohort

This study is not randomized, but patients will be stratified by age cohort and randomly assigned for assessment of PK to PK Schedule 1 or 2 (Section 3.5.2).

At least 24 patients evaluable for safety will be enrolled and treated within the following age cohorts:

- Cohort 1: young infants aged >28 days to <60 days (n=8)
- Cohort 2: term neonates (defined as gestational age ≥37 weeks) aged 7 to ≤28 days (n=8)
- Cohort 3: preterm neonates (defined as gestational age ≥34 to <37 weeks) aged 7 to ≤28 days (n=8).

#### 3.5.2. Assignment to PK schedule

Two PK samples (approximately 0.3 to 0.6 mL per draw) will be obtained at steady state from at least 20 patients. Patients will be randomly assigned (1:1) at the time of enrolment to one of the PK sample collection schedules:

- PK Schedule 1: at the end of the ceftaroline fosamil infusion (± 5 minutes) and 3 to 4 hours after the end of the infusion
- PK Schedule 2: 15 minutes to 2 hours after the end of the ceftaroline fosamil infusion and 5 to 7 hours after the end of the infusion (before the start of the next infusion)

### 3.6. Methods for ensuring blinding

This study is not blinded. The investigators, pharmacists or designees, study centre personnel, and parent(s)/legally-acceptable representative(s) will be aware of study therapy being administered.

### 3.7. Methods for unblinding

The study is not blinded.

### 3.8. Restrictions

Concomitant use of potentially effective systemic antibacterial therapy (other than study therapy), or any drug known to exhibit a contraindicated drug-drug interaction with any study therapy or labelled contraindication to use of any study therapy is not allowed.

### 3.9. Discontinuation of investigational product

At any time, parent(s) or legally-acceptable representative(s) are free to discontinue the patient from treatment with IP or withdraw the patient from the study (ie, IP and assessments – see Section 3.10.2), without prejudice to further treatment. Parent(s) or legally-acceptable representative(s) who decide to discontinue a patient from treatment with IP will always be asked about the reason(s) and the presence of any adverse events. If possible, the patient will be seen and assessed by an investigator(s). Adverse events will be followed up until SFU, 28 to 35 days after the last dose of study therapy (See Section 6). Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF.

#### 3.9.1. Procedures for discontinuation of a patient from investigational product

##### 3.9.1.1. Discontinuations Due to Safety

Assessments and Procedures: A patient who is prematurely discontinued from study therapy administration for safety reasons should have EOT assessments conducted per Section 4.2.5 and undergo subsequent assessments at TOC and SFU.

Clinical Outcome Assessment: If a patient is prematurely discontinued from study therapy due to an AE and the clinical signs and symptoms of sepsis have resolved completely or improved such that no further antibacterial therapy is necessary, the patient should be assessed as a clinical cure at EOT and reassessed at TOC.

If a patient is prematurely discontinued from study therapy due to a study therapy-related AE and requires alternative non-study antibacterial for treatment for LOS, the patient should be assessed as a clinical failure.

Reasons for premature discontinuation from study therapy administration due to safety may include, but are not limited to, occurrence of an AE that, in the opinion of the investigator, warrants the patient's permanent discontinuation from study therapy administration.

### 3.9.1.2. Discontinuations Due to Insufficient Therapeutic Effect

Assessments and Procedures: A patient who is prematurely discontinued from study therapy administration due to insufficient therapeutic effect should have EOT assessments conducted per Section 4.2.5 and undergo subsequent safety assessments at TOC and SFU.

If a patient is discontinued from study therapy administration due to insufficient therapeutic effect and is switched to an alternative IV antibiotic, that therapy should be documented.

Clinical Outcome Assessment: A patient who is prematurely discontinued from study therapy administration (at any time after the required minimum treatment duration of 48 hours) due to insufficient therapeutic effect should be assessed as a clinical failure on the day of discontinuation (ie, EOT). Such a patient will be automatically assigned an outcome of clinical failure at all subsequent evaluation time points.

Reasons: Reasons for discontinuation from study therapy administration due to insufficient therapeutic effect may include, but are not limited to, the following:

- Clinical Worsening: A patient who shows signs of clinical worsening may be discontinued from study therapy administration at any time. If the investigator deems the benefit-to-risk ratio of continuing study therapy acceptable, study therapy administration for at least 48 hours is encouraged before discontinuation

- Lack of Clinical Progress: For a patient who is stable, yet does not show signs of improvement, the investigator is encouraged to continue study therapy administration at least 48 hours before such a patient is assessed as a clinical failure and the patient is discontinued from study therapy

- Resistant Pathogen(s): If an organism resistant to one or more of the components of study therapy is isolated, the investigator will determine whether the patient remains on study therapy. If clinical improvement is observed in the setting of a resistant isolate, the patient may be kept on study therapy at the discretion of the investigator. Treatment with the study therapy should be discontinued if the patient develops a concomitant bacterial infection with an organism that is not susceptible to the study therapy and requires further parenteral therapy

- CNS Infection, Osteomyelitis, Endocarditis, or NEC: At Baseline, the investigator should use clinical judgment to determine whether an imaging study is indicated to rule out the presence of CNS infection (eg, meningitis, brain abscess, or subdural abscess), osteomyelitis, endocarditis, or NEC. If the patient is diagnosed with any of these conditions after enrolment into the study, the Medical Monitor should be notified, and the patient should be discontinued from study therapy, appropriately treated per standard of care, and be assessed as indeterminate.

If a patient is withdrawn from study, see Section 3.10.

### 3.10. Criteria for withdrawal

Assessments and Procedures: A patient may be withdrawn from the study at the request of his or her parent(s), legally-acceptable representative(s), the investigator, or Sponsor. A patient who is withdrawn completely from this study should be encouraged to undergo, if possible, EOT assessments per Section 4 on the day of withdrawal. Patients withdrawn from the study need not undergo subsequent TOC efficacy assessments.

Clinical Outcome Assessment: Patients who are withdrawn from the study and have not been assessed as clinical failure should be assessed as indeterminate for all remaining scheduled clinical assessments.

Reason(s) for withdrawal from the study may include, but are not limited to, the following:

- Lost to follow-up
- Withdrawal of consent
- Significant patient noncompliance, as judged by the investigator, defined as parent(s)/legally-acceptable representative(s) refusal or inability to adhere to study procedures
- Investigator determination that it is in the best interest of the patient to withdraw from the study, due to reasons other than an AE.

The investigator is encouraged to discuss with the Medical Monitor any extenuating circumstance that led to or may lead to withdrawal.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's source documentation. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

#### 3.10.1. Screen failures

Screen failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be included in the study. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures.

Where a patient is incorrectly started on treatment the patient may continue or discontinue treatment, depending on the outcome of the discussion between the Sponsor study physician/designee and the investigator.

### 3.10.2. Withdrawal of the informed consent

A parent/legally-acceptable representative is free to withdraw their child from the study at any time (IP and assessments), without prejudice to further treatment.

A parent/legally-acceptable representative who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The investigator will follow up AEs outside of the clinical study.

If the parent/legally-acceptable representative also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

If a parent/legally-acceptable representative withdraws their child from participation in the study, then the child's enrolment code cannot be reused. Withdrawn patients will be replaced.

### 3.11. Discontinuation of the study

The study may be stopped if, in the judgment of the Sponsor, trial patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug,
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the Case Report Form (CRF). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

### 3.12. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Investigator File.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subject's parent(s)/legal guardian/legally acceptable representative are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The

contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the global study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the global study team for advice on medical questions or problems that may arise during the study. The contact center contact number is not intended for use by the subject's parent(s)/legal guardian/legally acceptable representative directly; if a subject's parent(s)/legal guardian/legally acceptable representative calls that number, he or she will be directed back to the investigator site.

## 4. STUDY PLAN AND TIMING OF PROCEDURES

Study Day 1 will start at the onset of study therapy and will end 24 hours later. Subsequent Study Days are to follow the same pattern. Any time reference to a Study Day within the protocol is to be calculated in reference to the given Study Day at the time of onset of the first dose of study therapy (eg, within 24 hours of Day 3 means the period starting 24 hours before Day 3 at the onset time of study therapy up to 24 hours after Day 3 at the onset time of study therapy).

Procedures will be performed according to the Study Plan located in Table 1. The assessments and procedures should be conducted in person by the investigator or designee, unless otherwise indicated.

Results from any protocol-specified evaluations already performed locally as part of the patient's regular medical care can be recorded on the CRFs and do not have to be repeated for purposes of this study, as follows:

- Baseline clinical, laboratory, and microbiological tests: if performed within 36 hours of the first dose of study therapy
- Baseline chest radiograph (CXR), computed tomography (CT) scans, or other imaging tests: if performed as part of the patient's regular medical care within 72 hours of the first dose of study therapy
- After Baseline, any protocol-specified evaluations: if performed within 24 hours of any study day.

Table 1 provides an overview of the protocol visits and procedures. Refer to the Study Assessments section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

**Table 1 Study Plan detailing the procedures**

| | Assessment or Procedure | Baseline[a] | Treatment period | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Study Days* | | | | | | |
| | | | 1 | 2 | 3 | 4-14 | EOT[b] | TOC[c] | SFU[d] |
| | Written informed consent | X | | | | | | | |
| | Inclusion/exclusion criteria[e] | X | | | | | | | |
| Clinical | Medical history (including antepartum/peripartum period) | X | | | | | | | |
| Clinical | Adverse event review (AEs and SAEs) | X | X | X | X | X | X | X | X |
| Clinical | Prior and concomitant medications[f] | X | X | X | X | X | X | X | X |
| Clinical | Length | X | | | | | | | |
| Clinical | Weight | X | X | X | X | X | X | X | X |
| Clinical | Physical examination | X | X | X | X | X | X | X | |
| Clinical | Vital signs and oxygen saturation[g] | X | X | X | X | X | X | X | X |
| Clinical | Clinical outcome | | | | | | X | X | |
| Clinical | Record adjunctive therapeutic procedures (if performed) | | X | X | X | X | X | X | |
| Clinical | CXR, CT scan, or other imaging tests[h] | X[j] | | | | | | | |
| Laboratory | CBC with differential[i] | X | X[j] | | | | X | X[j] | X[j] |
| Laboratory | Chemistry panel[i] | X | X[j] | | | | X | X[j] | X[j] |
| Laboratory | Base excess | X[j] | | | | | | | |
| Laboratory | CRP and Procalcitonin[i] | X[j] | | | | | | | |
| Laboratory | Urinalysis | X | X[j] | | | | X | X[j] | |
| Laboratory | Urine output | X[k] | X | X | X | X[j] | | | |
| Laboratory | CSF | X[j] | | | | | | | |
| PK | Assignment to PK schedule[l] | X | | | | | | | |
| PK | PK blood sample[m] | | | | X | | | | |
| PK | CSF sample (if collected per standard of care) & matching blood sample[n] | | X | | | | | | |
| Micro | Blood culture | X[j] | | | | | | | |
| Micro | Urine culture | X[j] | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | CSF culture | | | | $X^j$ | | | | |
| | Other specimen or tissue cultures | | | | $X^j$ | | | | |
| | Administration of study therapy | | X | X | X | X | X | | |

* Study Day 1 will start at the onset of study therapy and will end 24 hours later. Subsequent Study Days are to follow the same pattern.

Abbreviations: AEs=adverse events; CBC=complete blood count; CRP=C-reactive protein; CSF=cerebrospinal fluid; CT=computed tomography; CXR=chest radiograph; EOT=End-of-Therapy; MRI=magnetic resonance imaging; PK=pharmacokinetic; SAEs=serious adverse events; SFU=Safety Follow-up; TOC=Test-of-Cure.

a. Conduct Baseline assessments within 36 hours before first dose of study therapy.
b. Conduct EOT assessments within 24 hours after the end of last infusion. Study therapy may or may not be given on the same calendar day as EOT assessments; administration should be as for days 4-14.
c. Conduct TOC assessments 8 to 15 days after the last dose of study therapy.
d. Conduct SFU assessments, preferably in person, 28 to 35 days after the last dose of study therapy. The SFU may be conducted via telephone for any patient who has not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC. If symptoms of relapse or new AEs or SAEs are noted, or at the discretion of the investigator, the patient should be immediately scheduled for an in-person visit. If the visit is in-person, weight, vital signs and oxygen saturation should be recorded. If a patient was previously assessed as a clinical failure, only safety assessments will be performed.
e. Refer to the inclusion criteria (Section 3.1) for the recommended definitions of clinical and laboratory inclusion criteria.
f. For patients who are being breast fed, record all medications taken by the lactating mother for 3 days before first dose of study therapy through SFU.
g. Postbaseline, record highest and lowest postdose temperature measurements.
h. At baseline, obtain results of CXR, CT scan, or other imaging tests (eg, echocardiogram, CT, MRI, sonography) if performed as part of the patient's regular medical care within 72 hours before first dose of study therapy.
i. Refer to the inclusion criteria (Section 3.1) for list of tests. Recommended to repeat at least every 7 days. If immature neutrophils are available, calculate I/T neutrophil ratio using the formula: I/T ratio=Immature cells/Total (mature+immature).
j. If clinically indicated.
k. For patients who have been hospitalized for ≥8 hours, calculate urine output over the last 8-hour period.
l. Patients will be randomly assigned (1:1) to one of the following PK sample collection schedules collected after any dose between the end of the 4th infusion of ceftaroline fosamil and before EOT or Study Day 14 (whichever is earlier):
   PK Schedule 1: at the end of the ceftaroline fosamil infusion (± 5 minutes) and 3 to 4 hours after the end of the infusion
   PK Schedule 2: 15 minutes to 2 hours after the end of the ceftaroline fosamil infusion and 5 to 7 hours after the end of the infusion (before the start of the next infusion).
m. PK blood samples are NOT to be drawn if the patient received a blood or blood component transfusion within the past 24 hours. For patients who are at risk from additional blood loss, collection of PK samples will require assessment by the investigator.
n. Matching blood sample to be collected only if 2 PK blood samples have not been collected already. The matching blood sample replaces one of the PK samples, so that the total number of PK samples does not exceed 2.

### 4.1. Baseline

Informed consent in writing will be obtained from parent(s) or legally-acceptable representative(s) before initiating any study assessment or procedure.

Baseline procedures must be completed within 36 hours before the start of the first dose of study therapy. If any such procedures have been carried out as standard-of-care within the timeframe they can be considered as baseline procedures. Potential patients who do not meet entrance criteria may, as appropriate, repeat Baseline evaluations at a later time for possible enrolment into the study.

#### 4.1.1. Baseline assessments

##### 4.1.1.1. Clinical assessments

- Obtain a complete medical and surgical history, including, but not limited to, history of delivery, antepartum and peripartum antibacterials, vaccinations, congenital abnormalities, and all active conditions and all conditions diagnosed after birth
- Identify, assess, and record any AEs and SAEs starting from the time that informed consent is obtained
- Record prior medications (Section 7.7) taken or received within 7 days before the first dose of study therapy. For children who are being breast fed, record all medications taken by the lactating mother during the 3 days before the first dose of study therapy.
- Record the findings of a complete physical examination, including, but not limited to:
    - Physical findings of LOS
    - Presence of central venous catheter (eg, umbilical catheter); evaluate the possibility of catheter-related sepsis (CRS) and if CRS is suspected, remove the catheter when it is safe and clinically feasible
    - Presence of other medical devices such as ventilator, cardiac devices, CSF shunts, orthopedic transplants, or urinary catheter
- Record weight and length
- Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation
    - Record at least 2 heart rate/pulse measurements taken during a 30 minute period

- Record at least 2 blood pressure measurements, or record highest and lowest measurements if continuously monitored, over a 30 minute period

- Record CXR or chest CT scan results if performed as part of the patient's regular medical care within 72 hours before the start of the first dose of study therapy

- Record other imaging study results (eg, echocardiogram, CT, MRI, sonography) if performed as part of the patient's regular medical care within 72 hours before the start of the first dose of study therapy.

#### 4.1.1.2. Laboratory assessments

- Obtain blood samples for complete blood count (CBC) with differential and chemistry panel (see Laboratory Manual)

- If blood gases are available, calculate base excess (BE) using the formula: BE=0.9287 (HCO3 24.4 + 14.83 (pH - 7.4))

- Record CRP and serum procalcitonin levels if tests are performed as part of the patient's regular medical care

- Perform urinalysis (see Laboratory Manual)

- For patients who have been hospitalized for ≥8 hours, calculate urine output over the last 8-hour period

- If clinically indicated and performed as part of patient's regular medical care, obtain CSF sample.

#### 4.1.1.3. Microbiological assessments

Microbiological assessments should be performed preferably before any antibiotics are administered.

- If clinically indicated and performed as part of patient's regular medical care, obtain blood and urine samples for testing per Section 5.2.1 and 5.2.2, respectively; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed

- If clinically indicated and performed as part of patient's regular medical care, obtain CSF or other specimens/tissue samples per Section 5.2.3 and 5.2.4, respectively; cultures may be repeated per standard of care upon knowledge of a positive result.

- Obtain any prior microbiological and clinical data (eg, notes in medical records confirming worsening of signs and symptoms of sepsis) that may help determine eligibility (Section 5.2)

Enrol the patient and assign to PK schedule after verifying that the patient meets all inclusion and no exclusion criteria. There should be no medically inappropriate delay in administration of study therapy.

### 4.2. Treatment period

Procedures for this period will be performed according to the schedule outlined in the Study Plan (Table 1) and the following are descriptions of specific requirements for the treatment period:

#### 4.2.1. Study Day 1 (starts with onset of study drug administration)

Study Day 1 is the 24-hour period starting at the onset of the first administration of study therapy. Baseline assessments may be conducted within 36 hours before the onset of study therapy; therefore, Study Day 1 procedures described below are to be conducted within 24 hours of the onset of study therapy.

##### 4.2.1.1. Study therapy administration

- Ceftaroline fosamil, IV: 6 mg/kg IV over 60 (± 10) minutes q8h (± 1 hour). The dose should be calculated based on the patient's first weight of the day.
- Ampicillin, IV: if mandated as per Section 7.2.2; dosage per institutional guidelines
- Optional aminoglycoside, IV: choice of aminoglycoside and dosage per institutional guidelines and investigator's judgment. Gentamicin is preferred.

##### 4.2.1.2. Clinical assessments - after at least 1 dose of study therapy

- Identify, assess, and record any new or ongoing AEs or SAEs
- Record concomitant medications (Section 7.7). For patients who are being breast fed, record all medications taken by the lactating mother.
- Record the findings of a complete physical examination, including, but not limited to, physical findings of LOS, presence of central venous catheter or other medical devices (if applicable)
- Record the patient's first weight of the day
- Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record highest and lowest postdose temperature measurements
- Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed

- If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the patient's regular medical care.

#### 4.2.1.3. Laboratory assessments - after at least 1 dose of study therapy

- If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual)
- If blood gases are available, calculate BE
- If clinically indicated, obtain CRP and serum procalcitonin levels
- If clinically indicated, perform urinalysis (see Laboratory Manual)
- For patients who have been hospitalized for ≥8 hours, calculate urine output over the last 8-hour period
- If clinically indicated and performed as part of patient's regular medical care, obtain CSF sample.

#### 4.2.1.4. Microbiological assessments - after at least 1 dose of study therapy

- If clinically indicated and performed as part of patient's regular medical care, obtain blood and urine samples for testing per Section 5.2.1 and 5.2.2, respectively; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.
- If a lumbar puncture (or any CSF sample collection) is performed after the first infusion of ceftaroline fosamil, a matching PK blood sample should be drawn at the time of CSF collection (± 5 minutes). This PK blood sample will replace the closest corresponding PK blood sample based on the PK times described above.
- If clinically indicated and performed as part of patient's regular medical care, obtain CSF or other specimens/tissue samples per Section 5.2.3 and 5.2.4, respectively; cultures may be repeated per standard of care upon knowledge of a positive result.

### 4.2.2. Study Day 2 (starts 24 hours after onset of study drug administration)

#### 4.2.2.1. Study therapy administration

- Ceftaroline fosamil, IV: 6 mg/kg IV over 60 (± 10) minutes q8h (± 1 hour). The dose should be calculated based on the patient's first weight of the day.
- Ampicillin, IV: if mandated as per Section 7.2.2; dosage per institutional guidelines
- Optional aminoglycoside, IV: choice of aminoglycoside and dosage per institutional guidelines and investigator's judgment. Gentamicin is preferred.

#### 4.2.2.2. Clinical assessments - any time during study day

- Identify, assess, and record any new or ongoing AEs and SAEs
- Record concomitant medications (Section 7.7). For patients who are being breast fed, record all medications taken by the lactating mother
- Record the findings of a complete physical examination, including, but not limited to, physical findings of LOS, presence of central venous catheter or other medical devices (if applicable)
- Record the patient's first weight of the day
- Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record highest and lowest daily temperature measurements
- Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed
- If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the patient's regular medical care.

#### 4.2.2.3. Laboratory assessments - any time during study day

- If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual)
- If blood gases are available, calculate BE
- If clinically indicated, obtain CRP and serum procalcitonin levels
- If clinically indicated, perform urinalysis (see Laboratory Manual)
- Calculate urine output over the last 8-hour period
- If clinically indicated and performed as part of patient's regular medical care, obtain CSF sample.

#### 4.2.2.4. PK procedures

- Do not draw PK blood samples if the patient received a blood or blood component transfusion within the past 24 hours. For patients who are at risk from additional blood loss, collection of PK samples will require assessment by the investigator.

- Obtain 2 PK blood samples after any infusion of ceftaroline fosamil, between the end of the fourth infusion and before EOT or Study Day 14 (whichever is earlier), according to the patient's assigned PK schedule shown below:

| | |
|---|---|
| **PK Schedule 1** | At the end of the ceftaroline fosamil infusion (± 5 minutes) |
| | 3 to 4 hours after the end of the infusion |
| **PK Schedule 2** | 15 minutes to 2 hours after the end of the ceftaroline fosamil infusion |
| | 5 to 7 hours after the end of the infusion (before the start of the next infusion) |

- If a lumbar puncture (or other CSF sample collection) is expected and the 2 PK blood samples have not been collected, the time of one of the PK blood samples should be adjusted to correspond to the time of the lumbar puncture; the total number of PK blood samples collected will not exceed 2.

- After the 2 PK blood samples have been collected, any portion of a CSF sample (collected as part of standard of care) not required for the patient's medical care should be retained for PK analysis.

#### 4.2.2.5. Microbiological assessments - any time during study day

- If clinically indicated and performed as part of patient's regular medical care, obtain blood and urine samples for testing per Section 5.2.1 and 5.2.2, respectively; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed.

- If clinically indicated and performed as part of patient's regular medical care, obtain CSF or other specimens/tissue samples per Section 5.2.3 and 5.2.4, respectively; cultures may be repeated per standard of care upon knowledge of a positive result.

### 4.2.3. Study Day 3 (starts 48 hours after onset of study drug administration)

#### 4.2.3.1. Study therapy administration

- Ceftaroline fosamil, IV: 6 mg/kg IV over 60 (± 10) minutes q8h (± 1 hour). The dose should be calculated based on the patient's first weight of the day.

- Ampicillin, IV: dosage per institutional guidelines (after 48 hours, the duration of treatment with ampicillin is at the discretion of the investigator)

- Optional aminoglycoside, IV: choice of aminoglycoside and dosage per institutional guidelines and investigator's judgment. Gentamicin is preferred.

#### 4.2.3.2. Clinical assessments - any time during study day

- Identify, assess, and record any new or ongoing AEs and SAEs
- Record concomitant medications (Section 7.7). For patients who are being breast fed, record all medications taken by the lactating mother
- Record the findings of a complete physical examination, including, but not limited to, physical findings of LOS, presence of central venous catheter or other medical devices (if applicable)
- Record the patient's first weight of the day
- Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record highest and lowest daily temperature measurements
- Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed
- If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the patient's regular medical care.

#### 4.2.3.3. Laboratory assessments - any time during study day

- If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual)
- If blood gases are available, calculate BE
- If clinically indicated, obtain CRP and serum procalcitonin levels
- If clinically indicated, perform urinalysis (see Laboratory Manual)
- Calculate urine output over the last 8-hour period
- If clinically indicated and performed as part of patient's regular medical care, obtain CSF sample.

#### 4.2.3.4. Microbiological assessments - any time during study day

- If clinically indicated and performed as part of patient's regular medical care, obtain blood and urine samples for testing per Section 5.2.1 and 5.2.2, respectively; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed

- If clinically indicated and performed as part of patient's regular medical care, obtain CSF or other specimens/tissue samples per Section 5.2.3 and 5.2.4, respectively; cultures may be repeated per standard of care upon knowledge of a positive result.

#### 4.2.3.5. PK procedures

- Do not draw PK blood samples if the patient received a blood or blood component transfusion within the past 24 hours. For patients who are at risk from additional blood loss, collection of PK samples will require assessment by the investigator.

- If not previously collected, obtain 2 PK blood samples after any infusion of ceftaroline fosamil, between the end of the fourth infusion and before EOT or Study Day 14 (whichever is earlier), according to the patient's assigned PK schedule (see Section 4.2.2.4 for schedule and adjustment for CSF sample collection).

### 4.2.4. Study Days 4 through 14 (starts 72 hours after onset of study drug administration and an extra 24 hours for each day thereafter)

#### 4.2.4.1. Study therapy administration

- Ceftaroline fosamil, IV: 6 mg/kg IV over 60 (± 10) minutes q8h (± 1 hour). The dose should be calculated based on the patient's first weight of the day.

- Ampicillin, IV: dosage per institutional guidelines (after 48 hours, the duration of treatment with ampicillin is at the discretion of the investigator)

- Optional aminoglycoside, IV: choice of aminoglycoside and dosage per institutional guidelines and investigator's judgment. Gentamicin is preferred.

#### 4.2.4.2. Clinical assessments - any time during study day

- Identify, assess, and record any new or ongoing AEs and SAEs

- Record concomitant medications (Section 7.7). For patients who are being breast fed, record all medications taken by the lactating mother

- Record the findings of a complete physical examination, including, but not limited to, physical findings of LOS, presence of central venous catheter or other medical devices (if applicable)

- Record the patient's first weight of the day, daily

- Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record highest and lowest daily temperature measurements

- Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed

- If clinically indicated, obtain results of CXR, CT scan, or other imaging test performed as part of the patient's regular medical care.

#### 4.2.4.3. Laboratory assessments - any time during study day

- If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual); recommended to repeat CBC with differential and chemistry panel at least every 7 days
- If blood gases are available, calculate BE
- If clinically indicated, obtain CRP and serum procalcitonin levels
- If clinically indicated, perform urinalysis (see Laboratory Manual) and calculate urine output over the last 8-hour period
- If clinically indicated and performed as part of patient's regular medical care, obtain CSF sample.

#### 4.2.4.4. Microbiological assessments - any time during study day

- If clinically indicated and performed as part of patient's regular medical care, obtain blood and urine samples for testing per Section 5.2.1 and 5.2.2, respectively; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed

- If clinically indicated and performed as part of patient's regular medical care, obtain CSF or other specimens/tissue samples per Section 5.2.3 and 5.2.4, respectively; cultures may be repeated per standard of care upon knowledge of a positive result.

#### 4.2.4.5. PK procedures

- Do not draw PK blood samples if the patient received a blood or blood component transfusion within the past 24 hours. For patients who are at risk from additional blood loss, collection of PK samples will require assessment by the investigator.

- If not previously collected, obtain 2 PK blood samples after any infusion of ceftaroline fosamil, between the end of the fourth infusion and before EOT or Study Day 14 (whichever is earlier), according to the patient's assigned PK schedule (see Section 4.2.2.4 for schedule and adjustment for CSF sample collection)

### 4.2.5. End-of-Therapy (EOT)

Conduct EOT assessments within 24 hours after administration of the last dose of study therapy. Conduct the EOT assessments in place of the regular study visit (eg, Study Days 4 to ≤14) assessments that would have been performed the day of that visit. If applicable, refer to guidance on when to end study therapy in Section 3.9.

If applicable, as study therapy may or may not be given on the same calendar day as EOT assessments, administer study therapy as described in Section 4.2.4.

#### 4.2.5.1. Clinical assessments - after the last dose of study therapy

- Identify, assess, and record any new or ongoing AEs and SAEs
- Record concomitant medications (Section 7.7). For patients who are being breast fed, record all medications taken by the lactating mother
- Record the findings of a complete physical examination, including, but not limited to, physical findings of LOS; presence of central venous catheter or other medical devices (if applicable)
- Record weight
- Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record highest and lowest daily temperature measurements
- Assess clinical outcome (per Table 5, Section 8.4.1)
- Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed
- If clinically indicated, obtain results of CXR, CT scan, or other imaging test performed as part of the patient's regular medical care.

#### 4.2.5.2. Laboratory assessments - after the last dose of study therapy

- Obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual)
- If blood gases are available, calculate BE
- If clinically indicated, obtain CRP and serum procalcitonin levels
- Perform urinalysis (see Laboratory Manual)
- If clinically indicated, calculate urinary output over the last 8-hour period
- If clinically indicated and performed as part of patient's regular medical care, obtain CSF sample.

#### 4.2.5.3. Microbiological assessments - after the last dose of study therapy

- If clinically indicated and performed as part of patient's regular medical care, obtain blood and urine samples for testing per Section 5.2.1 and 5.2.2, respectively; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed

- If clinically indicated and performed as part of patient's regular medical care, obtain CSF or other specimens/tissue samples per Section 5.2.3 and 5.2.4, respectively; cultures may be repeated per standard of care upon knowledge of a positive result.

### 4.3. Follow-up period

Procedures for this period will be performed according to the schedule outlined in the Study Plan (Table 1) and the following are descriptions of specific requirements for the Follow-up period:

#### 4.3.1. Test-of-Cure (TOC)

Conduct TOC assessments 8 to 15 days after administration of the last dose of study therapy.

#### 4.3.1.1. Clinical assessments

- Identify, assess, and record any new or ongoing AEs and SAEs

- Record concomitant medications (Section 7.7). For patients who are being breast fed, record all medications taken by the lactating mother

- Record the findings of a complete physical examination, including, but not limited to, physical findings of LOS, presence of central venous catheter or other medical devices (if applicable)

- Record weight

- Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record highest and lowest daily temperature measurements

- Assess clinical outcome (per Table 5, Section 8.4.1)

- Record adjunctive therapeutic procedures (eg, drainage of foci of infection), if performed

- If clinically indicated, obtain results of CXR, CT scan, or other imaging tests performed as part of the patient's regular medical care; if test was performed after EOT but before TOC, record the latest result.

#### 4.3.1.2. Laboratory assessments

- If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual)
- If clinically indicated, perform urinalysis (see Laboratory Manual)
- If clinically indicated, calculate urinary output over the last 8-hour period
- If clinically indicated and performed as part of patient's regular medical care, obtain CSF sample.

#### 4.3.1.3. Microbiological assessments

- If clinically indicated and performed as part of patient's regular medical care, obtain blood and urine samples for testing per Section 5.2.1 and 5.2.2, respectively; cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed
- If clinically indicated and performed as part of patient's regular medical care, obtain CSF or other specimens/tissue samples per Section 5.2.3 and 5.2.4, respectively; cultures may be repeated per standard of care upon knowledge of a positive result.

If a patient was previously assessed as a clinical failure, perform only safety assessments (ie, AEs and SAEs, concomitant medications, weight, vital signs, CBC with differential, chemistry panel).

### 4.3.2. Safety Follow-Up (SFU)

Conduct SFU assessments, preferably in person, 28 to 35 days after the last dose of study therapy. The SFU may be conducted via telephone for any patient who has not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC. If symptoms of relapse or new AEs or SAEs are noted, or at the discretion of the investigator, the patient should be immediately scheduled for an in-person visit. If a patient was previously assessed as a clinical failure, only safety assessments should be performed.

#### 4.3.2.1. If SFU conducted via telephone

- Record concomitant medications (Section 7.7). For patients who are being breast fed, record all medications taken by the lactating mother
- Identify, assess, and record any new or ongoing AEs or SAEs.

#### 4.3.2.2. If SFU conducted in person

**Clinical assessments**

- Identify, assess, and record any new or ongoing AEs or SAEs
- Record concomitant medications (Section 7.7). For patients who are being breast fed, record all medications taken by the lactating mother
- Record weight
- Record vital signs (heart rate/pulse, blood pressure, respiratory rate, temperature) and oxygen saturation; record highest and lowest daily temperature measurements.

**Laboratory assessments**

- If clinically indicated, obtain blood samples for CBC with differential and chemistry panel (see Laboratory Manual).

## 5. STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The global study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The investigator will ensure that data are recorded on the CRF as specified in the study protocol and in accordance with the CRF completion instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed CRF. A copy of the completed CRF will be archived at the study site.

### 5.1. Efficacy assessments

Efficacy outcome measures will include clinical outcome at EOT and TOC in the Modified Intent-to-Treat (MITT) Analysis Set. Clinical outcome will be assessed by the investigator Categories of clinical outcome are described in Section 8.4.1.1 and 8.4.1.2. A favourable clinical outcome is clinical cure.

## 5.2. Microbiological assessments

### 5.2.1. Blood sample for culture

If clinically indicated and performed as part of patient's regular medical care, obtain blood for culture at Baseline (preferably before any antibiotics are administered) and at any time through TOC. Cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed. Perform culture and organism identification at the local or regional laboratory, as applicable. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study-specific clinical and microbiology laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of blood culture or isolates.

This protocol complies with European Union's recommendations for blood loss associated with pediatric research[3] and the World Health Organization guidelines "Blood Sample Volumes in Child Health Research: Review of Safe Limits".[6] To minimize risk from blood loss associated with this study, standard of care laboratory results will be used whenever possible. All safety laboratory tests will be limited to local processing. In addition, pediatric blood collection tubes will be used and capillary method of blood draw will be implemented whenever feasible. PK samples will be collected from patients unless deemed unsafe due to the risk from additional blood loss (per the investigator's judgment).

### 5.2.2. Urine sample for culture

If clinically indicated and performed as part of patient's regular medical care, obtain urine for culture as clinically indicated at Baseline (preferably before any antibiotics are administered) and at any time through TOC. Cultures should be repeated per standard of care upon knowledge of a positive result until sterilization is confirmed. Perform Gram stain, culture, and organism identification at the local or regional laboratory, as applicable. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study-specific clinical and microbiology laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of urine culture or isolates.

### 5.2.3. Cerebrospinal fluid for culture

If clinically indicated and performed as part of patient's regular medical care, obtain CSF for culture and/or PCR as clinically indicated at Baseline (preferably before any antibiotics are administered) and at any time through TOC. Cultures may be repeated per standard of care upon knowledge of a positive result. Perform Gram stain, culture/PCR, and organism identification at the local or regional laboratory, as applicable. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study-specific clinical and microbiology laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of CSF culture or isolates.

### 5.2.4. Other specimens and tissue samples for culture

If clinically indicated and performed as part of patient's regular medical care, obtain other specimen and tissue samples from potential foci of infection for culture as clinically indicated at Baseline (preferably before any antibiotics are administered) and at any time through TOC. Cultures may be repeated upon knowledge of a positive result, if obtained per standard of care. Perform Gram stain (if applicable), culture, and organism identification at the local or regional laboratory. Send all isolates to the central laboratory for organism identification and susceptibility testing.

Refer to the study-specific microbiology and clinic laboratory manual for specific procedures pertaining to the collection, processing, storage, and shipment of other specimens/tissues for culture or isolates.

## 5.3. Safety assessments

Patients must be evaluated by a physician or an appropriately trained health care professional at every visit, and the evaluation must be documented. The procedures discussed below will be completed at the designated visits.

### 5.3.1. Laboratory safety assessments

Blood samples and urine samples will be collected according to the study plan (Table 1) at baseline and EOT. Samples may also be collected at any time during the treatment period, at TOC and SFU if clinically indicated.

The following laboratory variables will be measured:

**Table 2 Laboratory Safety Variables**

| Chemistry panel | CBC and differential | Urinalysis |
|---|---|---|
| Albumin | Haematocrit | Urinalysis will be done |
| Alkaline phosphatase | Haemoglobin | |
| Alanine aminotransferase | Red Blood Cell count | |
| Aspartate aminotransferase | White Blood Cell count | |
| Bilirubin, total and direct | Eosinophils[c] | |
| Blood urea nitrogen/urea | Lymphocytes[c] | |
| Calcium | Monocytes[c] | |
| Chloride | Neutrophils[c] | |
| Creatinine[a] | Neutrophils, immature[c] | |
| Glucose, nonfasting[a] | Platelets | |
| Potassium | | |
| Sodium | | |
| Bicarbonate ($HCO_3$)[b] | | |
| Lactate[b] | | |
| pH[b] | | |
| C-reactive protein[b] | | |
| Procalcitonin[b] | | |

a Required for eligibility
b Test not mandatory for eligibility if other eligibility criteria are met.
c absolute count and/or %

If a patient's urine output decreases to <0.5 mL/kg/h (measured over at least 8 hours) or serum creatinine level increases ≥2 × ULN during the treatment period, the Medical Monitor should be contacted to discuss the patient's safe continuation in the study. If a patient's haemoglobin or haematocrit decreases significantly (investigator's judgment) during study therapy, an evaluation for haemolytic anaemia should be conducted per standard of care.

Scheduled and clinically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local or regional laboratory.

### 5.3.2. Other clinical assessments

Safety parameters will be monitored according to standard medical practice and guidelines for IV administration of study therapy.

Vital sign assessments will be conducted at the specified time points outlined in the Study Plan (Table 1).

Medical and surgical history including antepartum/peripartum period, prior and concomitant medications, length, weight, and physical examination findings (including LOS physical findings and presence of central venous catheter or other medical devices) will be recorded at Baseline and, if applicable, during the study according to the Study Plan (Table 1).

If performed, adjunctive therapeutic procedures will be recorded throughout the treatment period until TOC.

If performed as part of the patient's regular medical care, results of CXR, CT scan or other imaging tests will be obtained at Baseline, throughout the treatment period, at EOT and at TOC.

#### 5.3.3. Adverse events

Adverse events will be reviewed at Baseline, throughout the Treatment Period, and at EOT, TOC and SFU. AEs and SAEs are defined in Section 1.1 and 1.3, respectively. AEs will be collected and reported as described in Section 1.1.

### 5.4. Pharmacokinetics

#### 5.4.1. Collection of blood samples

Two PK blood samples (approximately 0.3 to 0.6 mL per draw) will be obtained at steady state from at least 20 patients. Patients will be randomly assigned (1:1) at the time of enrolment to one of the PK sample collection schedules shown below. The PK samples may be collected anytime between the end of the fourth infusion of ceftaroline fosamil and before EOT or Study Day 14 (whichever is earlier). For patients who are at risk from additional blood loss, collection of PK samples will require assessment by the investigator.

If CSF sample collection is expected per standard of care, delay any PK sample collection and collect it at the time of CSF collection (± 5 minutes) as a matching PK blood sample. Record the time of the matching PK blood sample collection.

If the 2 PK blood samples have not been collected and a lumbar puncture (or any CSF sample collection) is performed after the first infusion of ceftaroline fosamil and within 8 hours after the last infusion, a matching PK blood sample will be drawn at the time of CSF collection (± 5 minutes). This PK blood sample will replace the closest corresponding PK blood sample based on the PK times described below. The total number of PK blood samples collected will not exceed 2.

| | |
|---|---|
| **PK Schedule 1** | At the end of the ceftaroline fosamil infusion (± 5 minutes) |
| | 3 to 4 hours after the end of the infusion |
| **PK Schedule 2** | 15 minutes to 2 hours after the end of the ceftaroline fosamil infusion |
| | 5 to 7 hours after the end of the infusion (before the start of the next infusion) |

The PK sampling time may be adjusted by the Sponsor based on emerging data, but the total number of samples will not be increased.

### 5.4.2. Collection of cerebrospinal fluid samples

For patients who have CSF collected as part of standard of care, the remainder of any CSF sample obtained after the first dose of ceftaroline fosamil will be retained to compare ceftaroline concentrations in the CSF to those in plasma. After the 2 PK blood samples have been collected, any portion of a CSF sample (collected as part of standard of care) not required for the patient's medical care should be retained for PK analysis.

Blood and CSF samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

### 5.4.3. Determination of drug concentration

Samples for determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 (inactive metabolite) concentrations in plasma and any available samples for determination of ceftaroline and ceftaroline M-1 concentrations in CSF will be analysed by Covance Laboratories on behalf of the Sponsor, using appropriate bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical report.

### 5.4.4. Storage and destruction of pharmacokinetic samples

PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report (CSR) but separately in a Bioanalytical Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be stored at a secure laboratory designated by the Sponsor; see details in the Laboratory Manual).

### 5.5. Pharmacodynamics (not applicable)

### 5.6. Pharmacogenetics (not applicable)

### 5.7. Biomarker analysis (not applicable)

### 5.8. Volume of blood

Table 3 shows the maximum volume of blood that will be drawn from each patient for the purposes of the study, apart from blood that is taken as part of patient's normal standard of care. The volume drawn for study purposes may be lower, as samples taken as standard of care will be used where possible. The combined volume of all blood samples taken from a patient by the end of the study for investigational laboratory tests (ie, CBC with differential, chemistry panel, and PK analyses) is to be no more than 2.4cc/kg or 10cc total whichever is less. Any deviation from this should be clinically justified.

**Table 3 Volume of blood per patient**

| Assessment or Procedure | | Baseline | Treatment period | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Study Days | | | | | | |
| | | | 1 | 2 | 3 | 4-14 | EOT | TOC | SFU |
| Laboratory | CBC with differential[a] | 0.5 ml | | | | | 0.5 ml | | |
| Laboratory | Chemistry panel[a] | 1.2 ml | | | | | 1.2 ml | | |
| PK | PK blood sample[b] | | | 1.2 ml | | | | | |
| Maximum blood volume required per protocol | | 1.7 ml | | 1.2 ml | | | 1.7 ml | | |

a These samples are likely to be required per standard of care
b 2 PK samples (0.6 ml each) to be taken during the period from Day 2 to Day 14, at the discretion of the investigator

## 6. ADVERSE EVENT REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

### 6.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2)

non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

| **Safety Event** | **Recorded on the CRF** | **Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness** |
|---|---|---|
| SAE | All | All |
| Non-serious AE | All | None |
| Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure | All (regardless of whether associated with an AE), **except occupational exposure** | Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE) |

All observed or volunteered events regardless of suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist

in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

### 6.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

### 6.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the parent(s)/legal guardian/legally acceptable representative. In addition, each parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

### 6.1.3. Withdrawal From the Study Due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

### 6.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the parent(s)/legal guardian/legally acceptable representative provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including SFU Visit.

#### 6.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

#### 6.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

### 6.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

### 6.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## 6.2. Definitions

### 6.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

### 6.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

### 6.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

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

### 6.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a

tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

### 6.3. Severity Assessment

| If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows: | |
|---|---|
| MILD | Does not interfere with subject's usual function. |
| MODERATE | Interferes to some extent with subject's usual function. |
| SEVERE | Interferes significantly with subject's usual function. |

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 6.4. Special Situations

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

#### 6.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the

following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

### 6.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Occupational exposure to the investigational product under study is reportable to Pfizer Safety within 24 hours of investigator awareness.

#### 6.4.2.1. Exposure During Pregnancy

Not applicable.

#### 6.4.2.2. Exposure During Breastfeeding

Not applicable.

#### 6.4.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

### 6.4.3. Medication Errors and Lack of Efficacy

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

| Safety Event | Recorded on the CRF | Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| Medication errors and lack of efficacy | All (regardless of whether associated with an AE) | Only if associated with an SAE |

#### 6.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength, or at the wrong infusion rate.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the CRF per CRF completion guidelines.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the CRF per CRF completion guidelines and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

#### 6.4.3.2. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

### 6.5. Study governance and oversight

The safety of all Pfizer clinical studies is closely monitored on an on-going basis by Pfizer and its representatives. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to Investigators.

#### 6.5.1. Data and Safety Monitoring Board

An external DSMB meeting is to be held at regular intervals to evaluate the safety of this study and other ongoing pediatric studies of ceftaroline fosamil. The role of the DSMB members is to evaluate the safety of the pediatric studies on an ongoing basis in order to determine whether any undue safety concerns are observed, and thus whether the studies should be allowed to continue enrolment. The recommendations made by the DSMB to alter the conduct of the study will be forwarded to the Sponsor for final decision. The Sponsor will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

A detailed DSMB charter will be prepared by the Sponsor and agreed to by all DSMB members before initiation of enrolment in this study. This charter will document the timing, membership, analysis content, and review procedures for each DSMB meeting. Safety information will be prepared in advance of each DSMB meeting by an independent reporting statistician. Safety analyses will include, at a minimum, summaries of study disposition and all AEs, SAEs, deaths, and discontinuations due to AEs, potentially clinically significant (PCS) laboratory results, and individual patient listings of selected safety data.

## 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is ceftaroline fosamil.

### 7.1. Identity of investigational product(s)

| Investigational product | Dosage form and strength |
|---|---|
| Ceftaroline fosamil | 600 mg powder for concentrate for solution for infusion |

#### 7.1.1. Ceftaroline Fosamil

Ceftaroline fosamil for injection, 600 mg per vial, is supplied as a sterile pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20 mL vial. The excipient L-arginine is added as an alkalizing agent to maintain the constituted solution between pH 4.8 and 6.5.

##### 7.1.1.1. Directions for Use

Vials of ceftaroline fosamil are constituted with 20.0 mL of sterile water for injection; the amount of solution containing the appropriate dose is further diluted in sterile normal saline before infusion. Refer to the Investigational Product Handling Manual for detailed information on ceftaroline fosamil preparation.

##### 7.1.1.2. Drug Storage

Vials containing unreconstituted ceftaroline fosamil are stored according to labelled requirements. Constituted and diluted infusion bags or bottles should be stored and used per the directions presented in the Investigational Product Handling Manual.

### 7.1.2. Ampicillin and Optional Aminoglycoside

Ampicillin (if mandated as per Section 7.2.2) is to be initiated at Baseline and to be administered for at least 48 hours (minimum duration of study therapy); after 48 hours, the duration of treatment with ampicillin is at the discretion of the investigator.

The use of an aminoglycoside is considered optional from Baseline through the entire study, ie, may be started and stopped at any time during the study at the discretion of the investigator.

Consult the product package insert, label, and local dosing guidelines for further information regarding dosage, administration, storage, maximum doses, contraindications, warnings, precautions, and AEs reported.

## 7.2. Dose and treatment regimens

Patients will receive a combination of IV ceftaroline fosamil and ampicillin, plus an optional aminoglycoside of choice as an empiric therapy for LOS. The total duration of study therapy is 48 hours (minimum) to 14 days (maximum). Note that study therapy administration using a home health care service is not permitted.

### 7.2.1. Ceftaroline fosamil

Ceftaroline fosamil is approved for use in adults; thus, treatment with ceftaroline fosamil is limited in pediatric patients to investigational use only. In this study, each patient will receive ceftaroline fosamil 6 mg/kg IV over 60 (± 10) minutes q8h (± 1 hour).

### 7.2.2. Ampicillin

Ampicillin (if mandated, see below) is to be initiated at Baseline and to be administered for at least 48 hours (minimum duration of study therapy); after 48 hours, the duration of treatment with ampicillin is at the discretion of the investigator.

If the presence of an organism that requires treatment with ampicillin cannot be excluded, then the use of IV ampicillin for the first 48 hours is mandatory. If the results of additional microbiology, PCR or other investigations indicate that ampicillin during the first 48 hours of treatment is not required, then its use is at the discretion of the investigator (note: the findings of any such investigations must be fully documented in the patient's source data).

### 7.2.3. Aminoglycoside

The use of an aminoglycoside is considered optional from Baseline through the entire study, ie, aminoglycoside may be started and stopped at any time during the study at the discretion of the investigator. Gentamicin is preferred.

### 7.2.4. Dose adjustment

Patients with moderately or severely impaired renal function at screening, defined as serum creatinine ≥2 × ULN for age, urine output <0.5 mL/kg/h (calculated from an 8-hour urine collection; for hospitalized patients), or requirement for dialysis, will not be enrolled in this study; thus, no ceftaroline fosamil, ampicillin, or aminoglycoside dose adjustments are expected to be required for renal impairment.

Ampicillin and/or aminoglycoside dose adjustments needed per the investigator's judgment should be made per institutional guidelines.

However, if the patient's serum creatinine level increases ≥2 × ULN or the urine output decreases to <0.5 mL/kg/h (calculated from an 8-hour urine collection), the Medical Monitor should be contacted with the option to miss or postpone dosing, or discontinue the study.

## 7.3. Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

## 7.4. Storage

All study drugs should be kept in a secure place with controlled access under appropriate storage conditions and in accordance with applicable regulatory requirements. The IP label specifies the appropriate storage.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations. This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be

considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

### 7.5. Compliance

All treatments will be administered by hospital staff during hospitalization. Treatment compliance will be documented by study staff in the CRF by recording the infusion date, time, and volume.

### 7.6. Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. It is the responsibility of the Pharmacist or designee to ensure that current records of study drug inventory and accountability are maintained. Records must be readily available for inspection by the Sponsor or Sponsor's Representative and applicable regulatory authorities.

Upon receipt of study therapy drugs, the Pharmacist or designee will acknowledge receipt, visually inspect the shipment, verify the number of vials shipped are received, and document the condition of the drugs received. Refer to the Investigational Product Handling Manual for additional information.

#### 7.6.1. Study drug handling and disposal

For general drug destruction (eg, left over drug at site), the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor, and all destruction must be adequately documented. Where at all possible the IP should be destroyed locally at site and a third party supplier for return and destruction should only be used where specific country regulations or local procedures state this is not possible. Documentation should be provided by PRA or the Sponsor identifying that this is the case. For investigational product associated with a recall, the Sponsor will determine what is to be destroyed. The Sponsor or its representative will manage the execution of destruction using standards acceptable to the Sponsor or its representative.

### 7.7. Concomitant and other treatments

All prior medications (taken or received within 7 days before the first dose of study therapy) and all concomitant medications (taken during the study), including, but not limited to, all antimicrobials, parenteral nutrition, and blood and blood-component transfusions will be documented. For patients who are being breast fed, all medications taken by the lactating mother for 3 days before first dose of study therapy through SFU will also be recorded.

Concomitant antibacterial therapy is not permitted except in the case of clinical failure.

### 7.7.1. Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the CRF.

## 8. STATISTICAL ANALYSES

### 8.1. Statistical considerations

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before database lock and analysis of the data.

### 8.2. Sample size estimate

The primary objective of this study is to evaluate safety and tolerability of ceftaroline in neonates and young infants aged 7 to <60 days with LOS and the study is not powered for inferential statistical analysis. The sample size (24 patients; 3 cohorts of 8 patients) is considered adequate to evaluate the safety of ceftaroline in neonates and young infants with LOS.

### 8.3. Definitions of analysis sets

Analysis sets are described below and in Figure 2.

### 8.3.1. Intent-to-treat analysis set

The Intent-to-Treat (ITT) Analysis Set will consist of all enrolled patients.

### 8.3.2. Safety analysis set

The Safety Analysis Set will be a subset of the ITT Analysis Set and will include all patients who receive any amount of ceftaroline fosamil.

### 8.3.3. Modified intent-to-treat (MITT) analysis set

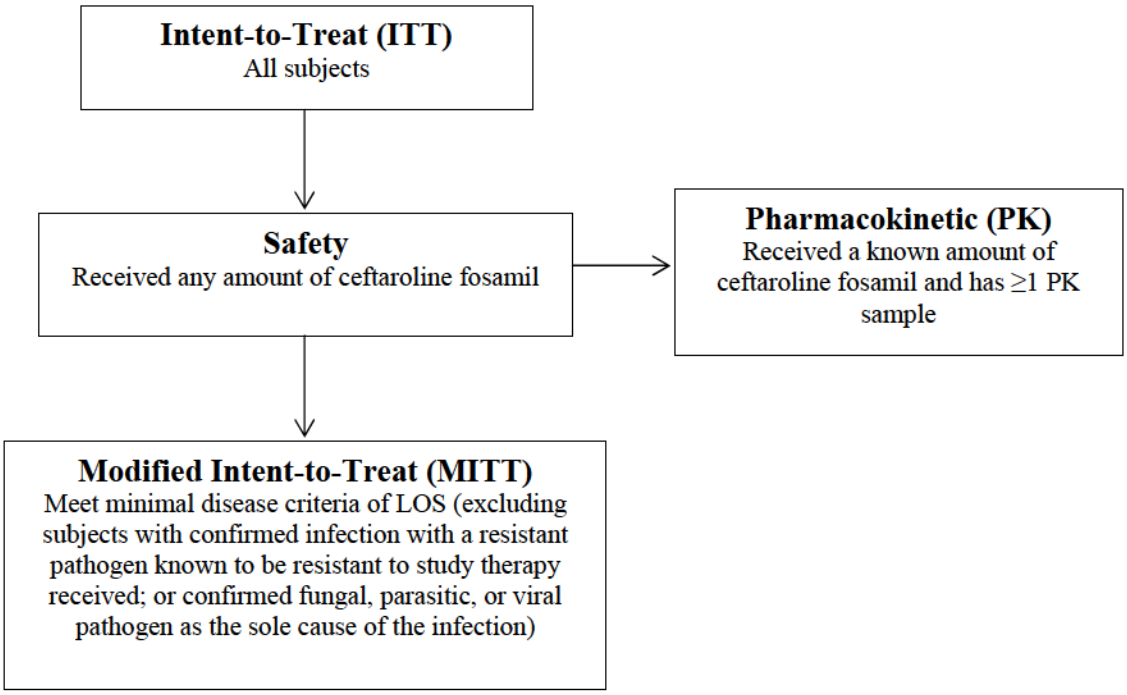
The MITT Analysis Set will include all patients who receive any amount of ceftaroline fosamil and who meet minimal disease criteria of LOS as described in the inclusion criteria in Section 3.1 (diagnosis of sepsis within 36 hours before enrolment, defined as the presence of at least 2 clinical criteria and at least 1 laboratory criterion in the presence of or as a result of suspected or proven bacterial infection that requires IV antibiotic therapy). Patients with confirmed infection with a pathogen known to be resistant to the study therapy received and patients with a confirmed fungal, parasitic, or viral pathogen as the sole cause of infection will be excluded. A list of resistant pathogens will be provided in the SAP.

### 8.3.4. Pharmacokinetic (PK) analysis set

The PK Analysis Set will include all patients who receive a known amount of ceftaroline fosamil and who have had at least 1 PK sample collected (excluding those receiving blood or

blood component transfusions within 24 hours before sample collection or who are at risk from additional blood loss per the discretion of the investigator).

**Figure 2 Study Analysis Sets**




## 8.4. Outcome measures for analyses

### 8.4.1. Efficacy response definitions

#### 8.4.1.1. Clinical outcome at End-of-Therapy

An assessment of clinical outcome will be made by the investigator at EOT. The clinical outcome categories are defined in Table 4. A favourable clinical outcome is clinical cure. An outcome of clinical failure at EOT will be carried forward to TOC.

**Table 4 Clinical outcome categories at End-of-Therapy**

| Outcome | Definition |
|---|---|
| Clinical Cure | Resolution of all acute signs and symptoms of LOS or improvement to such an extent that no further antibacterial therapy is required |
| Clinical Failure | Patients who received ≥48 hours of study treatment and meet any of the following:<br>• Discontinuation of study therapy due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, worsening in signs and symptoms of LOS, or isolation of a resistant pathogen that requires alternative nonstudy antibacterial therapy<br>• Discontinuation of study therapy due to a study therapy-related AE and requirement for alternative nonstudy antibacterial therapy for LOS<br>• Death in which LOS is contributory |
| Indeterminate | Study data are not available for evaluation of efficacy for any reason, including:<br>• Death in which LOS is clearly noncontributory<br>• Lost to follow-up<br>• Extenuating circumstances precluding classification as a cure or failure<br>• Diagnosis of CNS infection, osteomyelitis, endocarditis, or NEC at any time after enrolment<br>• Received <48 hours of study therapy |

Abbreviations: AE=adverse event; CNS=central nervous system; LOS=late-onset sepsis; NEC=necrotizing enterocolitis.

#### 8.4.1.2. Clinical outcome at Test-of-Cure

An assessment of clinical outcome will be made by the investigator at TOC. The clinical outcome categories are defined in Table 5. A favourable clinical outcome is clinical cure.

**Table 5 Clinical outcome categories at Test-of-Cure**

| Outcome | Definition |
|---|---|
| Clinical Cure | Resolution of all acute signs and symptoms of LOS or improvement to such an extent that no further antibacterial therapy is required |
| Clinical Failure | Patients who received ≥48 hours of study treatment and meet either of the following criteria:<br>• Incomplete resolution or worsening of LOS signs or symptoms or development of new signs or symptoms, or isolation of a resistant pathogen requiring alternative nonstudy antibacterial therapy<br>• Death in which LOS is contributory |
| Indeterminate | Study data are not available for evaluation of efficacy for any reason, including:<br>• Death in which LOS is clearly noncontributory<br>• Lost to follow-up<br>• Extenuating circumstances precluding classification as a cure or failure<br>• Diagnosis of CNS infection, osteomyelitis, endocarditis, or NEC at any time after enrolment<br>• Received <48 hours of study therapy |

Abbreviations: CNS=central nervous system; LOS=late-onset sepsis; NEC=necrotizing enterocolitis.

### 8.4.2. Microbiological response definitions

#### 8.4.2.1. Microbiological Outcome at Test-of-Cure

The per-pathogen microbiological outcome categories at EOT and TOC are defined in Table 6. Favourable microbiological outcomes are eradication or presumed eradication. Per-patient microbiological response at EOT and TOC will be determined programmatically based on individual outcomes for each baseline pathogen. In order for a patient to have a favourable microbiological response, the outcome for each baseline pathogen must be favourable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavourable (persistence or presumed persistence), the patient will be considered to have an unfavourable microbiological response.

Baseline pathogens will be determined based on central laboratory data. Rules for determination of pathogens will be described in the SAP.

**Table 6 Per-pathogen microbiological outcomes categories at End of Treatment and Test-of-Cure**

| Microbiological Response[a] | Definition |
|---|---|
| Eradication | Source specimen demonstrated absence of the original baseline pathogen |
| Presumed eradication | Source specimen was not available to culture and the patient was assessed as a clinical cure |
| Persistence | Source specimen demonstrates continued presence of the original baseline pathogen |
| Presumed persistence | Source specimen was not available to culture and the patient was assessed as a clinical failure |
| Indeterminate | Source specimen was not available to culture and the patient's clinical outcome was assessed as indeterminate |

a For patients who are clinical failures before TOC, the microbiological outcome will be carried forward to TOC and will be determined based on the cultures and/or clinical outcome at the time of the early clinical failure determination.

### 8.5. Methods for statistical analyses

Descriptive statistics (number, mean, SD, 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 summarized overall and by age cohort. Listings of individual patients' data will also be produced.

#### 8.5.1. Analysis of the study population and patient characteristics

Patient disposition (enrolment, discontinuations from the study) overall and within each age cohort will be provided based on the ITT Analysis Set. Reasons for exclusion from study analysis sets will be summarized for the ITT Analysis Set.

Demographics (age, race, gender), medical and surgical history including antepartum/peripartum period, baseline assessment of the clinical signs and symptoms of LOS, microbiological assessment of blood, CSF, urine, and other specimens or tissue samples will also be summarized for the ITT Analysis Set.

#### 8.5.2. Analysis of the primary variable

The safety analysis will be performed using the Safety Analysis Set and will include all patients who receive any amount of study therapy. Safety parameters include AEs, SAEs, deaths, clinical laboratory parameters (eg, CBC with differential, chemistry panel), and vital signs.

For each safety parameter, the last assessment made before the first dose of study therapy will be used as the baseline for all analyses. In the case of ECG where data are collected in triplicate, the mean of the three recordings will be considered as the baseline.

The incidence of AEs, SAEs, deaths, and discontinuations due to AEs will be summarized overall and within each age cohort, by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), by relationship to the study therapy, and by severity.

Descriptive statistics of observed results and the change from baseline will be presented for clinical laboratory results and vital signs. The incidence of selected PCS laboratory results will be summarized. A list of PCS results will be provided in the SAP.

### 8.5.3. Analysis of the secondary variables

Efficacy response will be analysed using the MITT Analysis Set. Proportions of patients with a favourable efficacy response will be displayed overall and within each age cohort. The number and percentage of patients classified as clinical cure at EOT and TOC will be tabulated in the MITT Analysis Set.

Microbiological success at EOT and TOCS will be evaluated. A summary of microbiological outcome by patient and by pathogen will be presented.

Every effort will be made to collect all data at specified times. A detailed description of the handling of dropouts and missing data for all efficacy and safety evaluations will be provided in the SAP.

#### 8.5.3.1. Pharmacokinetic sample collection and analyses

The PK data acquisition and analysis strategy in this study entails the use of a sparse PK sampling schedule, conducted only at selected investigational centres. Centres will be selected based on location, ability to conduct PK sampling procedures with accuracy, and ability to store and ship PK samples appropriately.

Pharmacokinetic sample handling and shipping procedures are described in the PK Sample Handling and Shipping Manual.

Concentrations of ceftaroline and ceftaroline M-1 in CSF will be presented.

Plasma concentrations of ceftaroline fosamil, ceftaroline and ceftaroline M-1 will be listed by age cohort. Ceftaroline plasma concentration data, along with other information including demographic data, will be combined with appropriate data from other clinical studies and analysed using a population PK approach and reported separately.

## 8.6. Interim Analysis

No formal interim analysis will be conducted for this study.

# 9. STUDY AND DATA MANAGEMENT

## 9.1. Training of study site personnel

A Co-ordinating Investigator will be selected from the investigators who will conduct the study (per European Union directive 75/318/EEC [as amended] Annex Part 4C).

Each investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any change to the protocol before seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or Competent Authority (CA). Each investigator will be responsible for enrolling only those patients who have met all of the protocol inclusion criteria and none of the exclusion criteria.

Before the first patient is entered into the study, a Sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the PRA Data Labs Electronic Data Capture (EDC) system utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 9.2. Monitoring of the study

During the study, the Sponsor representative will have regular contacts with the study site, conducted in accordance with current ICH E6 Good Clinical Practice (GCP) guidelines, and the respective United States or foreign regulations and guidelines, as applicable. Contacts will include visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The Sponsor representative will also be able to review query status remotely, which may warrant additional communication with the investigator and the study centre's personnel. The investigator will make available to the Sponsor representative source documents, signed ICFs, and all other study related documents. The Sponsor representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct

### 9.2.1. Source data

Refer to the CSA for location of source data.

Source documents may include, but are not limited to, study progress notes, study- or patient-specific e-mail correspondence, computer printouts, laboratory data, and recorded data from automated instruments. In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at the Sponsor that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

The original signed ICF for each participating patient shall be filed with records kept by the investigator. All documents produced in this study will be maintained by the investigator and made available for inspection by the Sponsor or Sponsor representative and applicable regulatory authorities.

### 9.2.2. Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between the Sponsor and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

### 9.2.3. Archiving of study documents

The investigator follows the principles outlined in the CSA.

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

**9.2.3.1. Data handling and record keeping**

Training sessions; monitoring of the investigative centre by the Sponsor or Sponsor representative; instruction manuals; and data verification, crosschecking, and auditing will be provided or performed to ensure quality of all study data. One or more investigator meetings will be held to prepare the investigator and other study personnel for appropriate collection of study data.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The Sponsor or Sponsor representative will review and validate study data as defined in the monitoring plan.

The Sponsor will provide the PI with a file in which to organize and retain all study-related documents. All study documents (including letters from the Sponsor or its representatives) should be retained in this file by the PI. The monitor will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by the Sponsor's auditor, regulatory authorities, or IRB.

It will be the responsibility of the investigator to ensure that the essential documents are available in the investigator's files or at the institutional centre. Any or all of these documents should be available for monitoring by the Sponsor or Sponsor representative and inspection by the regulatory authorities as defined in the monitoring plan.

### 9.3. Study timetable and end of study

The end of the study in all participating countries is defined as 'the last visit of the last patient undergoing the study' or date of study closure in the case of early study termination, whichever date is later.

#### 9.3.1. Study completion

The Sponsor requires the following data and materials before a study can be considered complete or terminated, including, but not limited to:

- Laboratory findings, clinical data, and all special test results from screening through SFU
- CRFs properly completed by appropriate study personnel and signed and dated by the investigator within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.
- Copies of complete study drug accountability records (eg, study drug inventory logs and shipment and return records)
- Copies of all IRB/IEC or CA approvals and acknowledgements
- A summary of the study prepared by the investigator (an IRB/IEC or CA summary letter is acceptable)

#### 9.3.2. Guidance to investigators on when to end study therapy

Patients who are improving clinically will receive at least 48 hours, but no more than 14 days, of study therapy. Before ending study therapy, patients should demonstrate improvement in the clinical assessment of their infection from Baseline as follows:

- Resolution of all acute signs and symptoms of LOS or improvement to such an extent that no further antibacterial therapy is necessary

- Microbiological eradication (confirmed or presumed).

An assessment of clinical outcome will be made by the investigator at the end of study therapy as defined in Section 4.2.5.

If signs and symptoms have not resolved or improved after 14 days, refer to Section 3.9.1.

### 9.3.3. Study termination by Sponsor and termination criteria

The Sponsor reserves the right to terminate an investigational site or this study at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies of ceftaroline indicates a potential health hazard to patients
- Serious or persistent noncompliance by the investigator with the protocol, clinical research agreement, Form FDA 1572, or applicable regulatory guidelines in conducting the study
- IRB/IEC or CA decision to terminate or suspend approval for the investigation or the investigator
- Investigator request to withdraw from participation
- Patient enrolment is unsatisfactory.
- Regulatory authority decision to terminate study
- Sponsor discontinues development of ceftaroline

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a reasonable timeframe (ie, two weeks). As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## 9.4. Data management

Data management will be performed by PRA according to the Clinical Informatics Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the Sponsor Drug Dictionary. Classification coding will be performed by the PRA Coding Group.

Data collection will involve the use of the PRA Data Labs EDC system, to which only authorized personnel will have access. Electronic CRFs will be used to capture study data in an EDC system. Entering of CRFs should be handled in accordance with instructions from the Sponsor or Sponsor representative. All CRFs must be completed by qualified study centre personnel. Each investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner.

Before the first patient is dosed at the investigational site, the Sponsor or Sponsor representative will meet with the investigator and the study centre's personnel to train them on recording the data on the CRFs using the EDC system. The investigator or designee will be responsible for reviewing CRFs, resolving data queries generated by the Sponsor via the system, providing missing or corrected data, approving all changes performed on the patient data, and endorsing these data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the Sponsor Drug Dictionary. All coding will be performed by the PRA Coding Group.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail. Queries may be issued electronically to the clinical study centre and answered electronically by that study centre's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable) will be collected.

The data will be validated as defined in the Clinical Informatics Plan and Edit Specifications Document. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Clinical Informatics Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records.

**Serious Adverse Event (SAE) Reconciliation**

SAE reconciliation between safety data and clinical data will be performed by PRA. The frequency depends on the expected volume of SAE reports and will be defined in the AE/SAE Reconciliation Plan.

## 10. ETHICAL AND REGULATORY REQUIREMENTS

### 10.1. Ethical conduct of the study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guidelines for Good Clinical Practices, and the Declaration of Helsinki.

### 10.2. Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

### 10.3. Ethics and regulatory review

An IRB/IEC should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer or its representative.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to the Sponsor before enrolment of any patient into the study.

The IRB/IEC should approve all advertising used to recruit patients for the study.

The Sponsor should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. The IRB/IEC or CA must approve any recruiting materials before use; and subsequent amended protocols and corresponding ICFs, before instituting amendment-specified changes to the study, unless required for patient safety. The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

The Sponsor or its representative will handle the distribution of any of these documents to the national regulatory authorities.

The Sponsor or its representative will provide Regulatory Authorities, Ethics Committees and PIs with safety updates/reports according to local requirements.

The investigator is responsible for informing the IRB/IEC or CA of any changes made to the protocol, and for advising the IRB/IEC or CA, at least once a year, about the progress of the study.

Each PI is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. The Sponsor or its representative will provide this information to the PI so that he/she can meet these reporting requirements.

### 10.4. Informed consent

This study will be conducted in compliance with current ICH E6 GCP pertaining to informed consent, the current CFR (Title 21, Parts 50 Subparts B and D, 56 and 312). The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. The Principal Investigator(s) at each centre will:

- Ensure each patient's parent(s) or legally-acceptable representative(s) is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient's parent(s) or legally-acceptable representative(s) is notified that their child is free to discontinue from the study at any time
- Ensure each patient's parent(s) or legally-acceptable representative(s) is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient's parent(s) or legally-acceptable representative(s) provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the investigator's Study File and is available for verification by the Sponsor or Sponsor representative at any time
- Ensure a copy of the signed Informed Consent Form is given to the patient's parent(s) or legally-acceptable representative(s)
- If applicable, the ICF will be provided in certified translation for non-English-speaking parent(s) or other legally-acceptable representative(s)

- Ensure that any reimbursement for study visits as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

### 10.5. Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator and the Sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment, and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and, if applicable, the national regulatory authority before implementation. Local requirements are to be followed for revised protocols.

Pfizer or its representative will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, the Sponsor or its representative and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

### 10.6. Audits and inspections

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, authorized representatives of Pfizer, or companies working on behalf of Pfizer, a regulatory authority, or an IRB/EC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator(s) will notify Pfizer or its agents immediately if contacted by a regulatory agency about an inspection at the centre. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be

present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

The investigator will allow the Sponsor or Sponsor representative and applicable regulatory authorities to inspect facilities and records relevant to this study. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

### 10.7. Reporting of safety issues and serious breaches of the protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### 10.8. Publication of study results

### 10.9. Communication of results by the Sponsor

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

### 10.9.1. Publications by investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

## 11. LIST OF REFERENCES

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## APPENDIX A INTERNATIONAL AIRLINE TRANSPORTATION ASSOCIATION (IATA) 6.2 GUIDANCE DOCUMENT

**Labelling and shipment of biohazard samples**

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

**Exempt** - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

# Document Approval Record

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