ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ:

<<ΜΕΘΟΔΟΛΟΓΙΑ ΒΙΟΪΑΤΡΙΚΗΣ ΕΡΕΥΝΑΣ, ΒΙΟΣΤΑΤΙΣΤΙΚΗ ΚΑΙ ΚΛΙΝΙΚΗ ΒΙΟΠΛΗΡΟΦΟΡΙΚΗ>>

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ:

<<A protocol for a superiority phase III randomized controlled trial for assessing the effectiveness of ceftaroline for treating Community-acquired Pneumonia in pediatric patients.>>

<<Πρωτόκολλο τυχαιοποιημένης κλινικής μελέτης, φάσης ΙΙΙ για την αξιολόγηση της αποτελεσματικότητας της κεφταρολίνης στη θεραπεία της πνευμονίας κοινότητας σε παιδιατρικούς ασθενείς.>>

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PROTOCOL INFORMATION PAGE

Trial Title:
A superiority, phase III, RCT for assessing the effectiveness of ceftaroline for treating Community acquired bacterial pneumonia in pediatric patients.

Trial Identification Number:
ClinicalTrials.gov Identifier: XXXXXXX
Study ID Number: XXXXXXX

Principal Investigator
XXXXXXX

Sponsor:
XXXXXX

Funded by:
XXXXXXX

Protocol Version Number:
Version 5.8

Date:
20 August 2019

PROTOCOL SIGNATURE PAGE

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol and GCP.

Principal Investigator	Signature	Site name or ID number	Date

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

Table of Contents

1. ABSTRACT

Introduction: Community-acquired bacterial pneumonia (CABP) remains a serious infection among children, despite the use of pneumococcal vaccination and it causes major morbidity and mortality in the pediatric population worldwide. Ceftaroline fosamil is a broad-spectrum cephalosporin antibiotic with activity against many bacteria, such as *Streptococcus pneumonia*, including penicillin-resistance and multidrug-resistant strains, and *Staphylococcus aureus,* including methicillin-resistant *S. aureus*.

Objective: The aim of this study is to assess the effectiveness and the safety of ceftaroline fosamil in the treatment of pediatric patients between 2 months and 16 years of age hospitalized with CABP.

Methods: This is a multicenter, randomized, phase 3, observer-blinded study. Overall, 250 participants will be randomized to receive either intravenous (IV) ceftaroline fosamil or ceftriaxone for 10 days. The primary efficacy endpoint is the proportion of patients with clinical cure at the test of cure visit. Secondary efficacy endpoints include the proportion of patients with: clinical and laboratory responses at study day 4, clinical cure at the end-of-treatment visit and clinical relapse at the late follow-up visit. The safety endpoint is the proportion of patients with adverse events and serious adverse events. For the statistical analysis of outcomes variables, x^2 test with 5% level of significance will be applied.

Key Words: ceftaroline fosamil, community-acquired bacterial pneumonia (CABP), hospitalization, pediatric, children, penicillin-resistance Streptococcus pneumoniae

1.1 Περίληψη

Εισαγωγή: Η βακτηριακή πνευμονία κοινότητας (ΒΠΚ) παραμένει μια σοβαρή λοίμωξη της παιδικής ηλικίας παρά τη χρήση εμβολίων έναντι του πνευμονιοκόκκου,η οποία προκαλεί σημαντική νοσηρότητα και θνησιμότητα στον παιδιατρικό πληθυσμό παγκοσμίως. Η κεφταρολίνη αποτελεί μια ευρέως φάσματος κεφαλοσπορίνη με δραστηριότητα έναντι πολλών βακτηρίων, συμπεριλαμβανομένου του Στρεπτόκοκκου της πνευμονίας και των στελεχών αυτού που είναι ανθεκτικοί στην πενικιλίνη ή είναι πολυανθεκτικά στα αντιβιοτικά αλλά και του χρυσίζοντα σταφυλόκοκκου, συμπεριλαμβανομένου του ανθεκτικού στην μεθικιλλίνη.
Σκοπός: Σκοπός αυτής της μελέτης είναι να αξιολογήσει την αποτελεσματικότητα και την ασφάλεια της κεφταρολίνης στη θεραπεία παιδιών ηλικίας 2μηνών έως 16 ετών που νοσηλεύονται με ΒΠΚ.
Μέθοδοι: Είναι μια πολυκεντρική,τυχαιοποιημένη κλινική μελέτη,φάσης 3,τυφλή για τους ιατρούς που αξιολογούν την κλινική πορεία των ασθενών. Συνολικά, 250 συμμετέχοντες ηλικίας 2 μηνών έως 16 ετών θα διαχωριστούν τυχαία ώστε να λάβουν ενδοφλέβια κεφταρολίνη ή κεφτριαξόνη για 10 ημέρες. Για την αξιολόγηση της αποτελεσματικότητας της κεφταρολίνης τα μετρά έκβασης διακρίνονται στο κύριο και στα δευτερεύοντα. Μέτρο κύριας έκβασης αποτελεί η αναλογία των ασθενών με κλινική ίαση κατά την επίσκεψη ελέγχου ίασης. Τα μέτρα δευτερεύουσας έκβασης συμπεριλαμβάνουν την αναλογία των ασθενών με: κλινική και εργαστηριακή ανταπόκριση την 4η ημέρα θεραπείας, κλινική ίαση στο τέλος της αγωγής και κλινική υποτροπή κατά την τελευταία επίσκεψη. Καταληκτικό σημείο για την αξιολόγηση της ασφάλειας της κεφταρολίνης αποτελεί η αναλογία των ασθενών με ανεπιθύμητες ενέργειες και σοβαρές ανεπιθύμητες ενέργειες. Για τη στατιστική ανάλυση θα εφαρμοστεί το χ2-τεστ με επίπεδο σημαντικότητας 5%.

Λέξεις-Κλειδιά: κεφταρολίνη, βακτηριακή πνευμονία κοινότητας (ΒΠΚ), νοσοκομειακή νοσηλεία, παιδιατρικός, παιδιά, ανθεκτικός στην πενικιλίνη Στρεπτόκοκκος της Πνευμονίας

1.2 Protocol synopsis

Title of study:	A multicenter, randomized, observer-blinded study for assessing the effectiveness of ceftaroline for treating Community acquired bacterial pneumonia in pediatric patients.
Clinical Phase:	**III**
Study Design:	An interventional, prospective, multicenter, observer-blinded, parallel, active controlled study. Eligible patients will be randomized to receive either intravenous (IV) ceftaroline fosamil or ceftriaxone for 10 days and they will be followed up until 45 days after the first dose of IV study drug in order to determine whether the ceftaroline is effective and safe for the treatment of CABP in pediatric patients.
Study Population:	Pediatric patients between 2 months and 16 years with CABP requiring hospitalization and IV antibiotic therapy.
Intervention:	IV Ceftaroline fosamil: • Children ≥ 6 months: 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg will be infused over 60 minutes every 8 hours. • Children < 6 months: 8 mg/kg over 60 minutes every 8 hours.
Control:	IV Ceftriaxone: • 75 mg/kg/day up to 4 g/day IV in equally divided doses each infused over 30 minutes every 12 hours.
Objectives:	**Primary Efficacy Objectives:** To determine the superiority of ceftaroline over ceftriaxone for the treatment of community acquired bacterial pneumonia in children between 2 months and 16 years old. **Secondary Efficacy Objectives:** To evaluate: • The clinical and laboratory response to ceftaroline at study day 4 • The effectiveness of ceftaroline at the end of treatment • The incidence of clinical relapse in the late follow up period **Safety Objectives:** To evaluate the safety of the ceftaroline for the treatment of community acquired bacterial pneumonia in children between 2 months and 16 years old.
Endpoints:	**Primary Efficacy Endpoint** • The proportion of patients with clinical cure at the test of cure (TOC) visit. **Secondary Efficacy Endpoints:** The proportion of patients with: • Clinical and laboratory response at study day 4 • Clinical cure at the end of treatment(EOT) visit • Clinical relapse at the late follow up(LFU) visit

	<u>Safety Endpoints</u> • Adverse events(AEs),Serious Adverse Events(SAEs),Laboratory variables, physical examination
Description of sites:	The study will take place in three General Children's Hospitals in Athens: "Agia Sophia", "Panagiotis & Aglaia Kyriakou", "Penteli's".
Eligibility Criteria	**Inclusion Criteria:** • Patients, male or female, between the ages of 2 months and 16 years. • Presence of CABP requiring hospitalization and IV antibacterial therapy. To meet the definition of CABP, children are required to have: (1) fever (temperature>38°C) or hypothermia (temperature <35°C) (2) the presence of new infiltrate(s) consistent with bacterial pneumonia, including a new alveolar/lobar infiltrate or consolidation (based on imaging results) and (3) acute onset or worsening within the previous 5 days of at least 2 of the following 9 clinical signs and symptoms: cough, tachypnea, dyspnea, grunting, sputum production, chest pain, cyanosis, evidence of pneumonia with parenchymal consolidation and increased work of breathing. • Children are required to have at least 1 of the 5 following laboratory findings: bacterial organism consistent with a typical respiratory pathogen identified or isolated from a respiratory (sputum and pleural fluid) or blood culture, leukocytosis (>15,000 white blood cells [WBC]/mm3), >15% immature neutrophils (bands) regardless of total peripheral white blood cell, leukopenia (4500WBC/mm3) and hypoxemia (oxygen saturation <92% on room air). • Female patients who have reached menarche are also required to have a negative urine pregnancy test, and those who are sexually active are required to be willing to practice sexual abstinence or dual methods of birth control during the treatment and for at least 28 days after the last dose of any study drug. • Prior to a subject's participation in the trial, the written informed consent should be signed and personally dated by the parents or legal guardians of each subject. Participants of appropriate intellectual maturity should personally sign and date a separately designed, written assent form prior entering the study. In Greece, the above written assent is required for minors who reached the age of ten years. **Exclusion Criteria:** • Admission to an intensive care unit for any period during the study. • Confirmed or suspected infection with a pathogen known to be resistant to ceftriaxone (e.g. Pseudomonas

	aeruginosa, MRSA), have a known infection at baseline with a sole atypical pathogen (e.g., M. pneumoniae, C. pneumoniae, Chlamydia trachomatis and Legionella pneumophila). • History of any hypersensitivity or allergic reaction to any β -lactam antimicrobial. • Patients considered at risk of MRSA infection at the discretion of the treating physician or with a predominance of Gram-positive cocci in clusters on sputum Gram stain. • Confirmed or suspected respiratory tract infection attributable to sources other than community-acquired bacterial pathogens (e.g., ventilator associated pneumonia and hospital-acquired pneumonia). • Non-infectious causes of pulmonary infiltrates on chest radiography or suspected sole viral, fungal or Mycobacterium tuberculosis infection (based on the judgment of the treating physician) of the lung, or chronic lung disease or neurologic disease that is preventing normal clearance of secretions. • Moderate or severe renal insufficiency (creatinine clearance <50 mL/min/1.73m^2 as calculated by using Schwartz bedside formula). • Patients who had received >24 hours of any systemic antibacterial therapy for an infectious disease within the 96 hours before randomization.
Randomization:	By using web software patients will be randomized applying both stratification and permuted blocks with random block sizes. Randomization will be stratified at each site based on the age. For this randomization scheme, one randomization list must be generated for each site and age group (12-16 years old, 6 years to<12 years, 24 months to <6 years, 2 months to <24 months). A sequence of block sizes is randomly generated where allowable block sizes will be 2, 4, or 6 in this study. Within each block, half of the assignments are randomly selected to be to the control group and remaining assignments are allowed to be to the intervention group. As each patient is randomized into the trial, the patient receives the next sequential assignment on the randomization list specific to his/her site and age group. The use of a random block size ensures that the next randomization assignment cannot be guessed. Because this is a multicenter trial with 3 sites, randomization within each site ensures that a site discontinuing participation in the trial or enrolling poorly would not affect the overall balance of the treatment groups. Stratifying by age group ensures that the control and intervention groups are balanced on this one important prognostic characteristic. The treatment groups will be nearly equal in size and will be balanced for age group.
Planned trial period	The study is expected to start in October 2019 and to end by October 2021. (2 years)

	Total duration of subject participation will be up to 45 days. Each individual will receive the investigational medicinal product (IMP) for 10 days. Three visits are scheduled after the completion of iv treatment and the exit from the hospital. The end-of-treatment visit (EOT) will take place at study day 11. The test-of cure-visit (TOC) will be at study day 21 +/- 4 days. Finally, the late follow up visit (LFU) will occur at study day 38 +/- 7 days.
Statistical Methods:	Power analysis was conducted for the estimation of the required sample size for this trial, so that the study would have adequate power to detect clinically meaningful differences between the two groups. Based on data from previous studies, the clinical cure rate is expected to be 89% for ceftriaxone. A difference of at least Δ=10% in response was considered as clinically important and the probability that the difference will be detected as statistical significant was set equal to 90% with a 5% level of significance. Assuming a 10% drop-out rate of the initial number of subjects enrolled to this trial, total number of 250 patients will have to be randomized. Demographics and baseline characteristics will be compared between groups using independent-sample t-test or non-parametric Mann Whitney U test for continuous variables and chi-square test for categorical variables. For the statistical analysis of both primary and secondary efficacy outcomes, chi-square test will be applied and the Odds ratio with the corresponding 95% Confidence will be calculated. Differences between treatment groups as regards to adverse event will be analyzed also by the chi-square test and serious adverse event will be analyzed by Fisher's exact test. The level of significance for all analyses is 5%. Two tailed P-values < 0.05 will be considered statistically significant. For data analysis, the statisticians will use SPSS statistical software (version 25). To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analysis will be performed for the factor "age" (12 years to 16 years, 6 years to <12 years, 24 months to <6 years, 2 months to <24 months in age). A single interim analysis of the primary outcome will be undertaken and reported to the Data Monitoring Safety Committee after 50% of participants have completed the study. The Haybittle-Peto stopping rule will be used as a guideline for the DSMC, where the DSMC may recommend the trial be stopped for early superiority if the P-value for difference between groups is ≤0.001. All analyses will follow the intention-to-treat principle. For missing data the "Last Observation Carried Forward" approach will be used.

1.3 List of Abbreviations

ADR	Adverse Drug Reaction
AEs	Adverse Events
CAP	Community Acquired Pneumonia
CABP	Community Acquired Bacterial Pneumonia
CDAD	Clostridium difficile-associated diarrhea
DSMC	Data Safety Monitoring Committee
EC	Executive Committee
eCRF	Electronic Case Report Form
EOT	End of (iv) treatment
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IBR	Institutional Review Board
ICF	Informed Consent Form
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
ITT	Intention to treat
IMPs	Investigational Medicinal Products
IV	Intravenous
LFU	Late follow up
LOCF	Last Observation Carried Forward
MDR	Multi-drug resistant
MRSA	Methicillin Resistant Staphylococcus Aureus
OR	Odds Ratio
PBPs	Penicillin-Binding Proteins
PI	Principal Investigator
PRSP	Penicillin Resistant Streptococcus Pneumoniae
SAEs	Serious Adverse Events
SC	Steering Committee
TOC	Test of cure

2. INDRODUCTION

2.1 Study Rationale

The aim of this study is to assess the effectiveness and safety of Ceftaroline fosamil compared with ceftriaxone in pediatric patients between 2 months and 16 years of age with community acquired bacterial pneumonia that requires hospitalization. Because of the increasing rate of antibiotic resistance in children, there is need for new effective antimicrobials to treat pediatric CABP, particularly for pneumonia caused by penicillin-resistant (PRSP) and multidrug resistant (MDR) Streptococcus pneumoniae, which remains a significant burden despite vaccination efforts.

2.2 Background

Pneumonia is the single largest infectious cause of death in children worldwide. Every year, it kills an estimated 1.4 million children under the age of five years, accounting for 18% of all deaths of children under five years old worldwide. [1]The World Health Organization estimates there are 156 million cases of pneumonia each year in children younger than five years, with as many as 20 million cases severe enough to require hospital admission. [2]

Community-acquired pneumonia (CAP) is defined as signs and symptoms of an acute infection of the pulmonary parenchyma in an individual who acquired the infection in the community, as distinguished from hospital-acquired (nosocomial) pneumonia.

Viruses cause a significant percentage of CAP infections, especially in children younger than two years. The prevalence of viral pneumonia decreases with age. [3] Respiratory syncytial virus, influenza A, and parainfluenza types 1 through 3 are the most common viral agents. Streptococcus pneumoniae remains the most frequent causative bacterial pathogen in children with CABP. Other bacterial pathogens include Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenza and Moraxella catarrhalis. Atypical pathogens in children include Mycoplasma pneumoniae and Chlamydophila pneumoniae.[4]After the introduction of conjugate pneumococcal vaccines, resistance to penicillin and ceftriaxone among pneumococcal isolates declined[5].However, PRSP, MDR S. pneumoniae, and an increased prevalence of invasive pneumococcal disease caused by serotypes not covered by the 13-valent pneumococcal conjugate vaccine (PCV13) remained a concern. Early results suggest that antibiotic resistance among S. pneumoniae isolates has continued to decline following the introduction of PCV13 but still remains an important consideration.[6] In addition, the incidence of CABP in children due to S. aureus, including methicillin-resistant S. aureus (MRSA), is on the rise.[7] Bacteria infecting children are particularly predisposed to antimicrobial resistance, with the highest prevalence of infections caused by penicillin-resistant S. pneumoniae occurring in those <2 years of age.[8]

According to the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America these are the recommendations on when does a child or infant with CAP require hospitalization [9]:
1. Children and infants who have moderate to severe CAP, as defined by several factors, including respiratory distress and hypoxemia (sustained saturation of peripheral oxygen [SpO2],90 % at sea level) should be hospitalized for management, including skilled pediatric nursing care. (Strong recommendation; high-quality evidence)
2. Infants less than 3–6 months of age with suspected bacterial CAP are likely to benefit from hospitalization. (Strong recommendation; low-quality evidence)

3. Children and infants with suspected or documented CAP caused by a pathogen with increased virulence, such as community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) should be hospitalized. (Strong recommendation; low quality evidence)
4. Children and infants for whom there is concern about careful observation at home or who are unable to comply with therapy or unable to be followed up should be hospitalized.
(Strong recommendation; low-quality evidence)

Ampicillin or penicillin G are the first-line treatment antibiotics recommended for fully immunized hospitalized pediatric patients with uncomplicated CABP.[9]For hospitalized children with uncomplicated CABP who are not fully immunized or who come from regions with high levels of penicillin-resistant invasive strains of pneumococcus, ceftriaxone or cefotaxime are recommended for empiric therapy.[9]If clinical, laboratory or imaging characteristics are consistent with infection caused by *S. aureus*, vancomycin or clindamycin are recommended in addition to β-lactam therapy.[9]

Ceftaroline, which is the active metabolite of the prodrug ceftaroline fosamil, is a fifth-generation cephalosporin with bactericidal effects. As a beta-lactam antibiotic, ceftaroline targets penicillin-binding proteins (PBPs) which are essential in the final steps of bacterial cell wall biosynthesis.[10][11] Moreover, it has a high affinity for modified PBPs, such as PBP2a in MRSA and PBP2x in PRSP, and is therefore active against these penicillin- resistant strains of bacteria and other multi-drug resistant pathogens.[12]

Ceftaroline has a broad-spectrum in vitro activity against both Gram-positive (such as Streptococcus and Staphylococcus) and Gram-negative organisms (Escherichia coli, Klebsiella and Haemophilus influenza). Like others cephalosporines, ceftaroline lacks coverage against enterococcal strains and does not provide coverage against pseudomonal infections. [13]

2.3 Benefit/Risk Assessments

2.3.1 Known potential benefits

Based on its mechanism of action and spectrum of activity, ceftaroline fosamil has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of adults with CABP or acute bacterial skin and skin structure infections. [14-17]

Surveillance data show that ceftaroline has in vitro activity against clinical isolates from pediatric patients. [18,19] Previous studies have shown that in children aged>2 months, ceftaroline fosamil is well tolerated with a safety profile reflective of the cephalosporin class.[20,21].However, there is sparse information available on the use of ceftaroline fosamil in pediatric patients, and ceftaroline fosamil does not currently have an indication for the use in this population group.

2.3.2 Known potential risks

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Before therapy with ceftaroline is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. [22, 23]

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ceftaroline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of C. difficile. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. [22, 23]

Direct Coombs' test seroconversion has been associated with cephalosporins and can lead to hemolytic anemia. If anemia develops during or after treatment with ceftaroline, drug-induced hemolytic anemia should be considered. Diagnostic studies including a direct Coombs' test should be performed. If drug-induced hemolytic anemia is suspected, discontinuation of ceftaroline should be considered and supportive care should be administered to the patient (i.e. transfusion) if clinically indicated. [22, 23]

2.3.3 Assessment of potential benefits and risks

Antibiotic resistance represents a growing cause of morbidity and mortality in health care, and this issue is further complicated in pediatric patients. Few antimicrobial agents have received approval to treat resistance pathogens while the rate of resistance for Gram-positive bacteria increases. Therefore, considering the broad spectrum of activity that ceftaroline has and especially the coverage that provides against MRSA and PRSP, it might be a potential therapeutic option for CABP in pediatric population. On the other hand, the potential risks can be identified and minimized by using procedures that are consistent with study design such as medical history, physical examination and laboratory exams. In addition, to minimize risk, those conducting the study are properly trained and experienced in studying the pediatric population, including evaluation and management of potential pediatric adverse events. To conclude, the risks to participants are reasonable in relation to the anticipated benefits that might be expected.

3. OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Efficacy Objectives

Primary Efficacy Objectives

To evaluate the effectiveness of ceftaroline for the treatment of community acquired bacterial pneumonia in children between 2 months and 16 years old.

Secondary Efficacy Objectives

To evaluate:

- The clinical and laboratory response to ceftaroline at study day 4
- The effectiveness of ceftaroline at the end of treatment
- The incidence of clinical relapse in the late follow up period

3.1.2 Safety Objectives

To evaluate the safety of the ceftaroline for the treatment of community acquired bacterial pneumonia in children between 2 months and 16 years old.

3.2 Endpoints

3.2.1 Efficacy Endpoints

Primary Efficacy Endpoint

- The proportion of patients with clinical cure at the TOC visit , in each treatment group.

Secondary Efficacy Endpoints:

The proportion of patients with:

- Clinical and laboratory response at study day 4
- Clinical cure at the EOT visit
- Clinical relapse at the LFU visit

in each treatment group.

3.2.2 Safety Endpoints

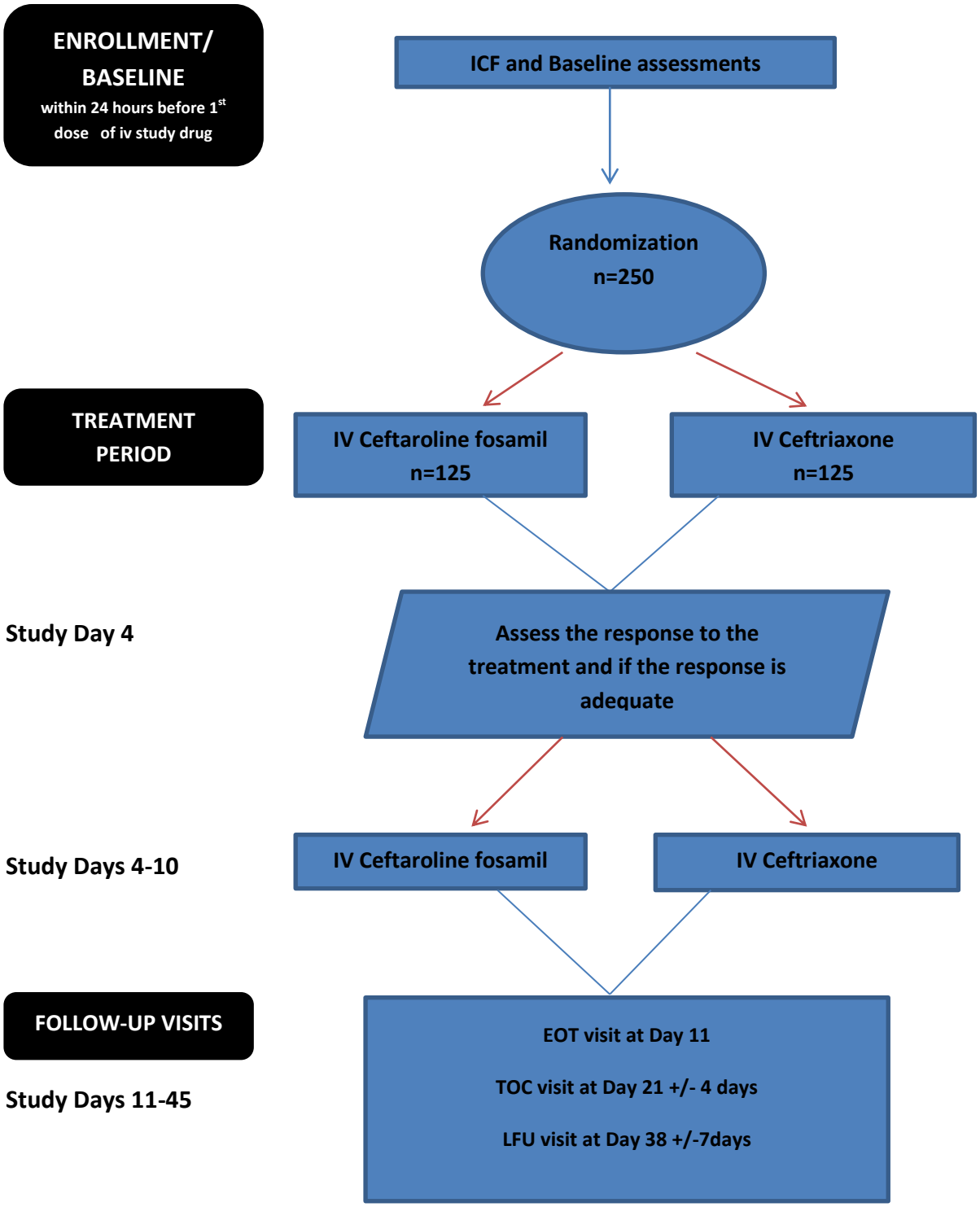
Adverse events (AEs), Serious Adverse Events (SAEs), Laboratory variables, physical examination

4. METHODS

4.1 STUDY DESIGN

This is a multicenter, superiority, phase III, randomized, prospective, observer blinded, parallel, comparator-controlled trial designed to assess the effectiveness of ceftaroline fosamil when administered to pediatric patients between 2 months and 16 years of age who are hospitalized with CABP. The study will take place in three General Children's Hospitals in Athens, Greece: "Agia Sophia", "Panagiotis & Aglaia Kyriakou" and "Penteli's". At enrollment data, will be collected including patient demographics, infection characteristics and pathogens. Approximately, 250 patients who meet the eligibility criteria will be randomized to receive either IV ceftaroline fosamil or ceftriaxone for 10 days. Study days are defined as the consecutive calendar days from the first day of study drug administration until the final study visit. On study day 4, the clinical and laboratory response to the given antibiotics will be evaluated and if the response is inadequate the study intervention will be discontinued. Three visits are scheduled after the completion of IV treatment and the exit from the hospital. The end-of-treatment visit (EOT) will take place at study day 11. The test-of cure-visit (TOC) will be at study day 21 +/- 4 days. Finally, the late follow up visit (LFU) will occur at study day 38 +/- 7 days.

4.1.1 Study flow chart



4.1.2 Study Population

Pediatric patients between 2 months and 16 years with CABP requiring hospitalization and IV antibacterial therapy who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

4.1.3 Inclusion Criteria

- Patients, male or female, between the ages of 2 months and 16 years
- Presence of CABP requiring hospitalization and IV antibacterial therapy. To meet the definition of CABP, children are required to have: (1) fever (temperature>38°C) or hypothermia (temperature <35°C); (2) the presence of new infiltrate(s) consistent with bacterial pneumonia, including a new alveolar/lobar infiltrate or consolidation (based on imaging results); and (3) acute onset or worsening within the previous 5 days of at least 2 of the following 9 clinical signs and symptoms: cough, tachypnea, dyspnea, grunting, sputum production, chest pain, cyanosis, evidence of pneumonia with parenchymal consolidation and increased work of breathing.
- Children are required to have at least 1 of the 5 following laboratory findings: bacterial organism consistent with a typical respiratory pathogen identified or isolated from a respiratory (sputum and pleural fluid) or blood culture, leukocytosis (>15,000 white blood cells [WBC]/mm3), >15% immature neutrophils (bands) regardless of total peripheral white blood cell, leukopenia (4500WBC/mm3) and hypoxemia (oxygen saturation <92% on room air).
- Female patients who have reached menarche are also required to have a negative urine pregnancy test, and those who are sexually active are required to be willing to practice sexual abstinence or dual methods of birth control during the treatment and for at least 28 days after the last dose of any study drug.
- Prior to a subject's participation in the trial, the written informed consent should be signed and personally dated by the parents or legal guardians of each subject. Participants of appropriate intellectual maturity should personally sign and date a separately designed, written assent form prior entering the study. In Greece, the above written assent is required for minors who reached the age of ten years.

4.1.4 Exclusion Criteria

- Admission to an intensive care unit for any period during the study.
- Confirmed or suspected infection with a pathogen known to be resistant to ceftriaxone (e.g., Pseudomonas aeruginosa, MRSA), have a known infection at baseline with a sole atypical pathogen (e.g., M. pneumoniae, C. pneumoniae, Chlamydia trachomatis and Legionella pneumophila).
- History of any hypersensitivity or allergic reaction to any β -lactam antimicrobial.
- Patients considered at risk of MRSA infection at the discretion of the treating physician or with a predominance of Gram-positive cocci in clusters on sputum Gram stain.
- Confirmed or suspected respiratory tract infection attributable to sources other than community-acquired bacterial pathogens (e.g., ventilator associated pneumonia and hospital-acquired pneumonia).
- Noninfectious causes of pulmonary infiltrates on chest radiography or suspected sole viral, fungal or Mycobacterium tuberculosis infection (based on the judgment of the treating physician) of the lung, or chronic lung disease or neurologic disease that is preventing normal clearance of secretions.
- Moderate or severe renal insufficiency (creatinine clearance <50 mL/min/1.73m^2 as calculated by using Schwartz bedside formula, see Appendix I).

- Patients who had received >24 hours of any systemic antibacterial therapy for an infectious disease within the 96 hours before randomization.

4.1.5 Study timetable and end of study

The end of the study is defined as the last visit of the last patient undergoing the study. The study is expected to start in October 2019 and to end by October 2021.The study may be terminated if the study procedures are not being performed according to GCP. Sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ceftaroline.

4.2 STUDY INTERVENTION

4.2.1 Description of investigational medicinal products

Investigational medicinal products (IMPs) will be manufactured in accordance with Good Manufacturing Practice (GMP).Both IMPs are in the form of a white to light yellow crystalline powder.

Investigational Medicinal Products	**Dose form and strength**	**Manufacturer**
Ceftaroline Fosamil	Powder for concentrate for solution for iv infusion, 400 mg.(20mL vial)	xxxxxxxx
Ceftriaxone	Powder for solution for iv infusion, 1 g/vial	xxxxxxxx

4.2.2 Dosage and Administration

This will be a parallel group study. Eligible patients will be randomly assigned to receive either ceftaroline fosamil or ceftriaxone for 10 days and randomization codes will be assigned strictly sequentially. The trial treatment will be administered by the Investigators who are not involved in the assessment of outcomes and only these will be aware of the treatment allocation. Pediatric patients over 6 months old will receive ceftaroline fosamil 12 mg/kg if weighing ≤33 kg or receive 400 mg ceftaroline fosamil if weighing >33 kg, infused over 60 minutes every 8 hours. Pediatric patients aged 6 months or younger will receive ceftaroline fosamil 8 mg/kg infused over 60 minutes every 8 hours. The doses of ceftaroline fosamil are based on pediatric population pharmacokinetic modeling design to achieve the same antibiotic exposure in children that is shown to be effective in adults. [24–26] Pediatric patients randomized to the comparator group will receive ceftriaxone 75 mg/kg/d to a maximum of 4 g/d, IV in equally divided doses, each infused over 30 minutes every 12 hours. The administration of all study drugs should be recorded in the appropriate sections of the electronic case report form (eCRF).

4.2.3 Labeling and Storage

Labeling of the IMPs will be designed in accordance with GMP and regulatory requirements of the country. In addition, the IMPs should be stored at the study centers in a secured facility with limited access, at 25ºC (77ºF), in the original package in order to protect from light.

4.2.4 Disposal and Handling

Both, the IMPs must be reconstituted with 20 ml of Sodium chloride 0.9 %(normal saline). Reconstituted solutions will take a pale yellow color. As regards ceftaroline fosamil, the reconstituted solution must be further diluted immediately in a range between 50 mL to 250 mL before intravenous infusion into patients and as a diluent 0.9% Sodium chloride injection should be used. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes. Once the intravenous solution is prepared with diluents it should be administered within 6 hours of preparation. Only clear solutions free of visible particles should be used. Standard aseptic techniques should be used for solution preparation and administration. The medicinal products must not be mixed with other drugs. Each vial is for single use only and any unused medicinal product or waste material should be disposed of in accordance with local requirements.

4.2.5 Accountability

The pharmacist will maintain accurate records of the receipt of all trial medication, including dates of receipt. In addition, accurate records will be kept regarding when and how much trial medication is dispensed and used by each participant in the trial. Reasons for departure from the expected dispensing regimen will be recorded. At the end of the trial, there will be final reconciliation of trial drug received, dispensed, consumed and returned. Any discrepancies will be investigated, resolved and documented by the trial team. Unused trial drug will be destroyed in compliance with applicable regulations.

4.2.6 Concomitant Therapy

The administration of any systemic antibacterial therapy except from the trial treatment is not permitted. In contrast, if any other concomitant therapies such as inhaled corticosteroids, bronchodilators, O_2, are considered essential for the improvement of clinical status of a participant, are allowed.

4.3 DISCONTINUATION AND WITHDRAWAL

4.3.1 Discontinuation of study intervention

Patients will be discontinued at any time from investigational product in the following situations:

1. Participant / legal guardian request to discontinue trial intervention.

2. Adverse event (AE) that in the opinion of the Investigator contraindicates further dosing.

3. Risk to patient as judged by the Investigator.

4. Eligibility requirement found not to be fulfilled.

5. No clinical and laboratory response to the treatment at Study day 4.

6. Development of any study specific criteria for discontinuation:

(a) Anaphylactic reaction to the investigational product requiring administration of epinephrine.

(b) Hemolytic anemia due to Direct Coombs' test seroconversion.

(c) Clostridium difficile-associated diarrhea

(d) Hy's Law: an indication that a medication is at high risk of causing fatal-drug induced liver injury. (Appendix II)

The reasons for premature discontinuation of IMPs should be recorded in the eCRF.
If a subject discontinues treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

4.3.2 Withdrawal from the study

Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrollment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

Withdrawal of the Informed Consent

Participant withdrawal from the trial should only occur if the participant or his/her legal guardians withdraw their consent to continue any trial involvement. This can occur at any stage of the trial following consent. Withdrawing from the trial will not affect their access to standard treatment or their relationship with the hospital and affiliated health care professionals. For the safety of all participants ceasing trial treatment, reasonable efforts should be made to undertake protocol-specified safety evaluations to capture new safety events and to assess existing, unresolved safety events following withdrawal. A dedicated Case Report Form (CRF) page will be used to capture the date of participant withdrawal of consent.

Losses to follow-up

A participant will be considered lost to follow-up if he or she fails to return for three scheduled visits (EOT, TOC, and LFU) and is unable to be contacted by the trial site staff. The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site will attempt to contact the legal guardians of the participant and reschedule the missed visit and counsel them on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the legal guardian of the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the last known email address). These contact attempts should be documented in the participant's medical record or trial file.

After, these actions if the participant continues to be unreachable, he or she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

4.3.3 Replacement of Subjects

Participants who sign the informed consent form and are not randomized / assigned trial intervention may be replaced. In contrast**,** participants who have been randomized / assigned trial intervention and discontinue treatment or withdraw from the study will not be replaced.

4.4 STUDY PROCEDURES AND ASSESSMENTS

The procedures and assessments that should be done at each stage of the study, including the three scheduled visits, are shown in the schedule below.

Schedule of procedures and assessments

Procedures/Assessments	**Enrollment/ Baseline Day -1**	**RANDOMIZATION**	**Days 1-3**	**Day 4**	**Days 5-10**	**EOT visit Day 11**	**TOC visit Day 21+/-3d**	**LFU visit Day 38+/-7d**
Informed Consent	X							
Assent Form	X							
Demographics	X							
Inclusion / Exclusion criteria	X							
Medical and Vaccination history	X							
Physical examination	X		X	X	X	X	X	X
Weight, Height, BMI	X							
Vital Signs (blood pressure, pulse, respiration rate, body temperature)	X		X	X	X	X	X	X
Oxygen saturation on room air	X		X	X	X	X	X	X
Serum chemistry	X		X	X	X	X	X	X
C-reactive protein test	X				X			
Hematology	X			X	X	X	X	X
Urinalysis	X			X	X		X	X
Direct COOMBS test			X	X	X	X	X	X
Urine pregnancy test	X					X	X	X
Creatinine Clearance	X			X	X	X	X	X
Blood Culture	X							
Sputum or Pleural Fluid Culture	X							
Serology test of IgM and IgG for atypal pathogens: Mycoplasma pneumonia, Chlamydophila pneumonia, Chlamydia trachomatis, Legionella pneumophilla	X							
Chest X-ray	X							
Administration of study drug			X	X	X			
Adverse Events			X	X	X	X	X	X
Efficacy Assessments				X	X	X	X	X
Safety Assessments			X	X	X	X	X	X

4.4.1 Enrollment

The maximum duration allowed between enrollment and randomization is 24 hours.
Firstly, the informed Consent Form (ICF) and in some cases an assent form must be signed prior to any procedures. Data that should be collected at baseline are demonstrated in Appendix III. After the procedures that must be done at enrollment, patients confirmed to be eligible will be randomized.

4.4.2 Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to a subject's participation in the trial, the written informed consent should be signed and personally dated by the parents or legal guardians of each subject and by the investigator or a person designed by the investigator who conducted the informed consent discussion. Information about the trial will be given in both oral and written form and subjects' legal representatives must be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the trial. Where appropriate, participants should assent to enroll in a study. Participants of appropriate intellectual maturity should personally sign and date a separately designed, written assent form prior entering the study and after being informed to the fullest extent possible about the study in language and terms they are able to understand. In all cases, participants should be made aware of their rights to decline to participate or to withdraw from the study at any time. In Greece, the above written assent is required for minors who reached the age of ten years [28]. A copy of the signed and dated informed consent form and the assent form will be given to the legal representative of the subject and the original will be maintained with the subject's records.

4.4.3 Randomization

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized and randomization codes will be assigned strictly sequentially in each stratum. By using web software patients will be randomized applying both stratification and permuted blocks with random block sizes. Randomization will be stratified at each site/center based on the age. For this randomization scheme, one randomization list must be generated for each site and age group (12-16 years old, 6 years to<12 years, 24 months to <6 years, 2 months to <24 months). A sequence of block sizes is randomly generated where allowable block sizes will be 2, 4, or 6 in this study. Within each block, half of the assignments are randomly selected to be to the control group and remaining assignments are allowed to be to the treatment group. As each patient is randomized into the trial, the patient receives the next sequential assignment on the randomization list specific to his/her site and age group. The use of a random block size ensures that the next randomization assignment cannot be guessed. Because this is a multicenter trial with 3 sites, randomization within each site ensures that a site discontinuing participation in the trial or enrolling poorly would not affect the overall balance of the treatment groups. Stratifying by age group ensures that the control and intervention groups are balanced on this one important prognostic characteristic. The treatment groups will be nearly equal in size and will be balanced for age group.

4.4.4 Blinding and code-breaking

The study will be observer-blinded with the assessment of clinical outcome being conducted by blinded staff, not involved in the administration of treatment. Each center will have at least one blinded investigator who will not know each patient's assigned treatment. Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigators and pharmacists at the study

center. The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator is to document and report the action to sponsor, without revealing the treatment given to patient. Sponsor retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

4.4.5 Efficacy assessments

Efficacy outcome measures will involve assessments of clinical and laboratory response at Study Day 4, clinical cure at the EOT and TOC visits and of the clinical relapses at LFU visit.

On study day 4, the clinical and laboratory response to the given antibiotics will be evaluated and if the response is inadequate the study intervention will be discontinued. Clinical response is defined as having improvement in at least two of the following symptoms: cough dyspnea, chest pain, sputum production, chills or rigors, feeling of warmth /feverish and exercise intolerance or lethargy and worsening of none of them. Laboratory response is defined as having white blood cell count within normal range for age or >20% improvement from baseline.

Clinical cure is defined as resolution of all acute symptoms of CABP or improvement of signs and symptoms to an extent that no further antimicrobial therapy is required, otherwise is considered as clinical failure.

Clinical relapse is defined as reappearance or worsening of signs and symptoms of CABP that required further antimicrobial therapy between TOC visit and LFU visit.

4.4.6 Safety assessments

Safety outcome measures will involve assessments of adverse events (AEs) and serious adverse events (SAEs) and clinical assessments including vital signs, temperature, physical examination findings and oxygen saturation. All AEs will be collected from the signing of the informed consent until 35 days after the last dose of the study drug. Safety laboratory assessments will include hematology testing of hemoglobin, hematocrit, red blood cell count, WBC count, WBC differentials (neutrophils, immature neutrophils, lymphocytes, monocytes, basophils and eosinophils percentage and counts) and platelet count. Serum chemistry testing will include albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin, bicarbonate, creatinine, glucose, potassium and sodium. Additional assessments will include C-reactive protein test, Direct Coombs' test, urine pregnancy test (in female patients who had reached menarche) and creatinine clearance (using the Schwartz bedside formula). Any clinically necessary laboratory testing and other procedures will be done per standard of care.

4.4.7 Sample Handling

The Principal Investigator is to ensure that samples are labeled in accordance with the Laboratory Manual and the Biological Substance. The Principal Investigator at each study center is to keep full traceability of collected biological samples from the patients while in storage at the study center until disposal. The sample receiver should be able to trace the samples while in storage and during use until used or disposed of and is to keep documentation of receipt of arrival. Sponsor will maintain oversight of the entire life cycle

through internal procedures, monitoring of study centers and auditing of external laboratory providers. Samples will not be retained for any future use such as a new clinical study.

4.5 SAFETY REPORTING

4.5.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

4.5.2 Definition of Serious adverse events

A serious adverse event (SAE) is an AE occurring during any study phase that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent any of the outcomes listed above.

4.5.3 Definition of Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to the administration of a medicinal product which is noxious and unintended, with a causal relationship between the drug and the reported reaction being a reasonable possibility.

4.5.4 Recording of adverse events

All AEs, including SAEs, will be collected from the time the informed consent is signed throughout the treatment period and including the follow-up period, until 45 days after the first dose of the study drug. The Investigator will probe, via discussion with the subject or his/her legal guardian, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the subject eCRF and will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study medication, or if unrelated, the cause.

4.5.5 Severity of Adverse Event

SEVERITY	Description
Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Serious	Any medical occurrence that can have as a result death, permanent disability/incapacity, is life-threatening or requires hospitalization or prolongation of an existing hospitalization.

4.5.6 Causality Assessment

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug. The relationship of the event to the trial intervention will be assessed as follows:

- Unrelated: There is no association between the trial intervention and the reported event. AEs in this category do not have a reasonable temporal relationship to exposure to the test product, or can be explained by a commonly occurring alternative aetiology.
- Possible: The event could have cause or contributed to the AE. AEs in this category follow a reasonable temporal sequence from the time of exposure to the intervention and/or follow a known response pattern to the test article, but could also have been produced by other factors.
- Related: The AE is a consequence of administration of the trial intervention. AEs in the category cannot be explained by concurrent illness, progression of disease state or concurrent medication reaction. Such events may be widely documented as having an association with the test product or that they occur after rechallenge.

4.5.7 Reporting of serious adverse events

If any SAE occurs in the course of the study, then Site Principal Investigator is responsible for reporting SAE to the Sponsor within 1 day, i.e., immediately but no later than 24 hours from when he or she becomes aware of it. These reports should be submitted using the trial Safety Report Form (SRF). In addition, reporting of SAEs to the Independent Review Board (IRB) will be performed by the PI in accordance with the standard operating procedures and policies of the IRB.

4.6 STATISTICAL CONSIDERATIONS

4.6.1 Sample size estimation

Power analysis was conducted for the estimation of the required sample size for this trial, so that the study would have adequate power to detect clinically meaningful differences between the two groups. Based on data from previous studies, the clinical cure rate is expected to be 89% for ceftriaxone. A difference of at least Δ=10% in response was considered as clinically important and the probability that the difference will be detected as statistical significant was set equal to 90% with a 5% level of significance. Thus, the clinical cure rate with ceftaroline is anticipated to be 99%.

$$\mathbf{n} \geq \left(\frac{p1(1-p1)+p2(1-p2)}{\Delta^2}\right) * (1.96 + 1.28)^2$$

$$\mathbf{n} \geq \frac{(0.89*0.11)+(0.99*0.01)}{0.1^2} * (1.96 + 1.28)^2 = 113.16$$

Consequently, at least 114 patients should be entered in each group. Assuming a 10% drop-out rate of the initial number of subjects enrolled to this trial, total number of 250 patients will have to be randomized.

4.6.2 Analysis Population

All analyses will be performed using an Intent-to-Treat (ITT) approach. All patients randomized and receiving any IMP will be included in the analysis, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

For dealing with missing data that derived from drop-outs the “Last Observation Carried Forward” approach will be used. Data for the last known state of the subject will be included in the analysis, assuming that is valid information about the subject’s true outcome.

4.6.3 Statistical Analysis

Demographics and baseline characteristics will be compared between groups using independent-sample t-test or non-parametric Mann Whitney U test for continuous variables and chi-square test for categorical variables. For the statistical analysis of both primary and secondary efficacy outcomes, chi-square test will be applied and the Odds ratio with the corresponding 95% Confidence interval will be calculated. Differences between treatment groups as regard to adverse event will be analyzed also by the chi-square test and serious adverse event will be analyzed by Fisher’s exact test. The level of significance for all analyses is 5%. Two tailed P-values < 0.05 will be considered statistically significant. For data analysis, the statisticians will use SPSS statistical software (version 25).

4.6.4 Subgroup Analysis

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analysis will be performed for the factor “age” (12 years to 16 years, 6 years to <12 years, 24 months to <6 years, young infants and toddlers from 2 months to <24

months in age). Data will be analyzed using a chi-square test, similar to the primary analysis and the same output will be presented for each subgroup as for the primary analysis.

4.6.5 Interim analysis

A single interim analysis of the primary outcome will be undertaken and reported to the Data Safety Monitoring Committee after 50% of participants have completed the study. The Haybittle- Peto stopping rule will be used as a guideline, where the DSMC may recommend the trial be stopped for early superiority if the P value for difference between groups is ≤0.001.

4.7 DATA MANAGEMENT

4.7.1 Source Data

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. If the eCRF is the site of the original recording (e.g. there is no other written or electronic record of data), eCRF entries will be considered source data. All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

4.7.2 Access Data

Direct access will be granted to authorized representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

4.7.3 Data Recording

Data will be collected at enrolment, during the hospitalization-administration of the IMP and at the follow up visits. All data will be entered at the study sites into a central database using an electronic case report form (eCRF), specifically designed for the purpose of the study, with a delegated Contract Research Organization (CRO) as an administrator. This eCRF will contain information such as demographic characteristics, medical history, clinical data, laboratory results, charts, pharmacy records, radiographs obtained during the patient's participation in the current study. In addition, adverse events (AEs, SAEs), discontinuations and clinical relapses will be recorded in eCRF .The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will not be included in any trial data electronic file. Data from this study will be stored until 15 years after trial completion, in accordance with the local ethics requirements.

4.8 MONITORING

Regular monitoring will be performed according to the trial specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements .During the study, monitors who are sponsor's representative will have regular contacts with the study center, including visits to:

- Verify that the investigators have adequate qualifications and resources and remain adequate throughout the trial period, that facilities including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
- Verify that the storage conditions for the IMP are acceptable and study drug accountability checks are being performed.
- Confirm that the investigational team is adhering to the protocol.
- Verify that written informed consent was obtained before each subject's participation in the trial and only eligible subjects were enrolled.
- Verify that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
- Check the accuracy and completeness of the eCRF entries, source documents and other trial-related records against each other.

4.9 STUDY COMMITTEES

4.9.1 Executive Committee

The Executive Committee will consist of members of the academic leadership of the study and 1 member from the sponsor. The EC will be responsible for the proper design and conduct of the study, ethical and professional standards of the trial and for considering and implementing any recommendations from the Data Safety Monitoring Committee. In addition, EC will be responsible for developing publication procedures and resolving authorship issues.

4.9.2 Steering Committee

The role of the Steering Committee (SC) is to provide the overall supervision of the trial. Ideally, the SC should include members who are independent of the investigators, their employing organizations, funders and sponsors. The SC should monitor trial progress and conduct and advice on scientific credibility.

4.9.3 Independent Data Safety Monitoring Committee (DSMC)

This study will be conducted under the auspices of an independent Data Monitoring Safety Committee (DSMC), which will monitor the progress of the study and ensure that the safety of subjects enrolled in the study is not compromised. The DSMC will have a chairperson and include at least 2 pediatricians, a pediatric pulmonologist as well as a biostatistician, who have experience in the conduct and monitoring of randomized controlled trials. Members of the DSMC will be independent of trial conduct. This committee will review accumulating data on a regular basis and may request access to unblinded data if needed. The DSMC will make recommendations to the Executive Committee and Sponsor regarding the continuing safety of subjects currently enrolled and yet to be enrolled in the trial.

4.10 ETHICAL AND REGULATORY REQUIREMENTS

4.10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization/Good Clinical Practice and applicable local ethical and legal regulatory requirements.

4.10.2 Institutional Review Boards / Independent Ethics Committees

The protocol and ICF will be reviewed and approved by the IRB/IEC. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed for the progress of the study. The Investigator will obtain a list of IRB members or other assurance of compliance with regulations. Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

4.10.3 Protocol Amendments

This trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, trial design, participant safety, or may affect a participants willingness to continue participation in the trial is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the IRB/IEC, for approval prior to being implemented.

4.10.4 Patient Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating participants. The trial protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records. All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified

only by the participant Identification Number (ID) to maintain participant anonymity. Clinical information will not be released without written permission of the participant, except as necessary for monitoring or regulatory agencies.

4.10.5 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, or an Ethics Committee may perform audits or inspections at the study centers, 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, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization , and any applicable regulatory requirements. The Investigator will contact sponsor immediately if contacted by a regulatory agency or other body about an inspection or an audit at the study center

4.10.6 Publication

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

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4.12 APPENDICES

4.12.1 APPENDIX I

Creatinine-Based "Bedside Schwartz" formula [27]

eGFR = 0.413 x (height/Scr) if height is expressed in centimeters
OR
eGFR =41.3 x (height/Scr) if height is expressed in meters

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m2
Scr (standardized serum creatinine) = mg/dL

4.12.2 APPENDIX II

Elevated Liver Chemistry Values and Criteria for potential drug-induced liver injury/Hy's Law

Parameter	**Criterion**
AST	≥3xULN
ALT	≥3xULN
Total bilirubin	≥2xULN
Potential Hy's law	AST or ALT≥3 x ULN and Total bilirubin ≥2xULN and ALP <2x ULN

ULN: Upper limit of normal AST: aspartate aminotransferase
ALP: Alkaline phosphatase ALT: alanine aminotransferase

4.12.3 APPENDIX III

Baseline patient demographics

Patient Demographic	Ceftaroline Fosamil	Ceftriaxone
Sex		
Male, n(%)		
Female, n(%)		
Age, years		
Median(range)		
Age group(range)		
12y-16y, n (%)		
6y-<12y, n (%)		
2y-<6y, n (%)		
2m-<2y, n (%)		
Weight (kg)		
Mean(SD)		
Height(m)		
Mean(SD)		
Body Mass Index(kg/m^2)		
Mean(SD)		
Race		
Caucasians, n (%)		
Others, n (%)		
Creatinine Clearance, mL/min/1.73m^2		
Mean(SD)		
≥50 mL/min/1.73m^2, n (%)		

Disease Characteristics and Radiographic Assessments

Disease Characteristics	Ceftaroline Fosamil	Ceftriaxone
History of pneumococcal vaccination, n (%)		
C-Reactive Protein(mg/dl)		
Mean(SD)		
Radiographic Assessments		
Pleural effusion, n (%)		
Unilateral		
Bilateral		
Lobes involved in pulmonary infiltrate, n (%)		
One lobe		
Multiple lobes		