Clinical Trial Protocol

Study Drug: Ceftaroline Fosamil

Study Title: Phase 1/2 Trial of Ceftaroline for the Treatment of Hematogenously Acquired *Staphylococcus aureus* Osteomyelitis in Children

Phase: Phase 1/2

Sponsor Investigator: Sheldon L. Kaplan
1102 Bates Avenue, Suite1150
Houston, TX 77030
Telephone: 832-824-4330
Fax: 832-825-4347

Funding: Allergan

Research Nurse: Andrea Forbes, MS, BSN, RN
Telephone: 832-824-4336
Fax: 832-825-4347
E-mail: aforbes@bcm.edu

Version Date: **v5.0 (**08October2018)

1. SUMMARY

Sponsor Investigator: Sheldon L. Kaplan, MD
Sponsor: Baylor College of Medicine
Funding: Allergan
Product Name: Ceftaroline
Protocol Title: Phase 1/2 Trial of Ceftaroline for the Treatment of Hematogenously Acquired *Staphylococcus aureus* Osteomyelitis in Children
Clinical Phase: 1/2
Objectives: **Primary:** • Evaluate the safety of ceftaroline in pediatric subjects 1 to 17 years of age (inclusive) with acute hematogenous osteomyelitis at the end of intravenous therapy. **Secondary:** • Evaluate efficacy of ceftaroline in pediatric subjects with acute hematogenous osteomyelitis at the end of IV therapy, at the end of total therapy (anticipated to be at 4 to 6 weeks after enrollment), and at one year after enrollment. • Evaluate clearance of *S. aureus* bacteremia if blood cultures initially positive. • Assess proportion of patients with plasma levels of ceftaroline that exceed 1 µg/mL for over 60% of a dosing interval.
Study Design: This is a Phase 1/2, open-label, single-center study to determine safety and tolerability of ceftaroline in pediatric subjects 1 to 17 years of age (inclusive) with signs and symptoms of acute hematogenous osteomyelitis at the end of intravenous therapy. After informed consent/assent is obtained, ceftaroline will be administered intravenously. After the subject has been afebrile for at least 48 hours, has negative blood cultures, is clearly improving in general, is able to eat and drink, and is able to use or move the involved extremity, the subject may be switched to oral antibiotic administration.
Number of Subjects: 18 Children 1 to 17 years of age, inclusive. Each subject will receive ceftaroline. 2 subjects above 5 years old will be enrolled before the younger subjects are enrolled.
Planned Study Period: Approximately 60 months (funding approval to last subject last visit). 6 subjects/year enrollment is anticipated.
Treatment Duration with ceftaroline: Approximately 5 to 14 days.
Subject Participation: The duration of subject participation from signing the informed consent form will be up to 14 months (includes screening period, study drug administration, oral drug administration and a follow-up visit 12 months after the last dose of study drug). Baseline assessments for study eligibility will occur within 24 hours before the first dose of study drug except for Alkaline Phosphatase, Bilirubin, AST/ALT which will be obtained prior to administration of ceftaroline but the results may not be available. A minimum of 2 days (48 hours) of study drug administration is required to assess safety.

Test Product, Dosage, and Mode of Administration: IV ceftaroline fosamil **15 mg/kg** (or 600 mg if > 40 kg) infused over 120 (± 10) minutes q8h (± 1 hour) for children **2 years** of age **– 17 years** of age (inclusive). IV ceftaroline fosamil **10 mg/kg** infused over 120 (± 10) minutes q 8h (± 1 hour) for children from **1 year of age to < 2 years** (inclusive).

Isolate susceptibilities: The ceftaroline MIC of *S. aureus* isolates or other isolates such as Group A streptococcus, *Streptococcus pneumoniae* or *Kingella kingae* that are obtained from the patients with acute hematogenous osteomyelitis will be determined using Clinical and Laboratory Standards Institute (CLSI) methods. These will be performed in the CAP certified Infectious Disease Research Laboratory. CLSI interpretive breakpoints will be used to determine if the isolate is susceptible, intermediate or resistant to ceftaroline.

Oral Switch: A switch to one of the following open-label PO drugs is expected/allowed on or after EOIV assessments are completed and if criteria in Section 9.2 are met:

- PO clindamycin 13 mg/kg/dose q8h in subjects with proven MRSA infection due to clindamycin susceptible MRSA or if no pathogen is isolated.

OR

- PO cephalexin 25 to 33 mg/kg/dose q 8 hours in subjects with proven MSSA infection.

OR

- PO linezolid 600 mg q12h (Children > 12 years old) or 10 mg/kg q8h (children ≤ 12 years old) in subjects with clindamycin-resistant MRSA pathogens or for patients with MRSA isolates who are unable to tolerate clindamycin.

Inclusion Criteria: Subjects are required to meet the following inclusion criteria:

1. Informed consent in writing from parent(s) or other legally acceptable representative(s) and assent from subject (if appropriate according to local requirements).
2. Male or female 1 to 17 years of age.
3. Suspected hematogenous SA osteomyelitis in a large bone (upper or lower extremities, pelvis) based on clinical findings and radiology results.
4. One to three sites of osteomyelitis with expectation that transition to oral antibiotics will be likely prior to discharge to complete IV therapy (The second or third site might be contiguous like a proximal tibia and distal femur but could also be at sites unrelated such as a distal femur and pelvic bone).
5. Female subjects who have reached menarche must have a negative urine pregnancy test.
6. Female subjects who have reached menarche and are sexually active must be willing to practice sexual abstinence or dual methods of birth control (eg, condom or diaphragm with spermicidal foam or gel) during treatment and for at least 28 days after the last dose of any study drug.
7. Sufficient IV access to receive medication.

Exclusion Criteria: Subjects must **NOT** meet any of the following exclusion criteria. Septic arthritis contiguous to the site of osteomyelitis is not an exclusion criterion.

1. Received more than 24 hours of IV antibiotics prior to enrollment.
2. More than three bones infected.
3. Disseminated infection or is admitted to the pediatric intensive care unit.
4. Underlying condition (excludes mild eczema or reactive airways disease).
5. Suspected or proven venous thrombosis or concern for endocarditis.
6. Requirement for other reasons for another antibiotic potentially active against organisms commonly causing osteomyelitis in children.
7. Creatinine clearance < 50 mL/min/1.73m2 (calculated by the Schwartz formula).
8. AST or ALT > 3 times the upper limit of normal.
9. Neutropenia (<500 neutrophils/mm^3).
10. Thrombocytopenia (<50,000 platelets/mm^3).
11. Females who are currently pregnant or breast feeding.
12. Hypersensitivity reaction to any Beta-lactam antibiotic.
13. Has had an allergic reaction to ceftaroline in the past.

Safety: Adverse event and serious adverse event monitoring, vital signs and laboratory tests (CBC,BUN, Creatinine, Alkaline Phosphatase, Bilirubin, AST and ALT will be obtained within 24 hours prior to enrollment and weekly during ceftaroline treatment and at the completion of ceftaroline treatment). The Alkaline Phosphatase, Bilirubin, AST/ALT results may not be available prior to enrollment of the patient. We do not anticipate that the AST/ALT concentrations will be > 3 UNL but if they were to be this elevated, the subject will be dropped from the study immediately.

Efficacy:

- Clinical response by subject and by baseline pathogen at the conclusion of IV ceftaroline.
- Clinical outcome at the completion of total therapy (IV plus oral)
- Clinical outcome at one year after enrollment into study-long-term follow-up.

Pharmacokinetics: The pharmacokinetic (PK) outcome measures will include concentrations of ceftaroline, ceftaroline fosamil (prodrug), and ceftaroline M-1 (inactive metabolite) in plasma in subjects on days 2 to 5 of treatment (only one PK sample collected on days 2-5) 4 hours (+/- 30 minutes) after the end of the infusion (before the start of the next infusion). Efforts will be made to obtain 1 PK blood sample (approximately 0.6 mL) at steady state from all subjects who receive ceftaroline fosamil. PK samples may be collected after any infusion of ceftaroline fosamil on those days and before oral switch.

If purulent material is being obtained from bone or subperiosteal abscesses at surgery or via drainage by interventional radiology, we will attempt to obtain specimens for measurement of ceftaroline concentrations.

Statistics:

- Descriptive statistical methods will be used to summarize the demographic characteristics of the subjects as well as selected clinical features such as duration of fever or positive blood cultures, time until normalization of ESR and CRP.
- The proportion of children with plasma concentrations of ceftaroline that exceed 1µg/mL at 4 hours following a 2 hour infusion of ceftaroline dose will be determined.
- Safety analyses will be conducted on all subjects who received at least one dose of ceftaroline. The occurrence of adverse events especially diarrhea, rash and evidence of bone marrow suppression which are the most common adverse effects associated with cephalosporin antibiotics will be evaluated.

Table 1.1 - Schedule of Assessments and Procedures

Assessment or Procedure	***Baseline*** [1]	***Treatment***					***Follow-up***
		Day 1	Days 2-14	End of IV Treatment (EOIV)	Week 2, Week 4, and Week 6 After Discharge[14]	End of Antibiotic Treatment (EOT)	Month 12
Obtain Informed Consent/Assent	X						
Verify Inclusion/Exclusion Criteria	X						
Demographic Data	X						
Medical and Surgical History	X				X	X	X
Complete Physical Examination[3]	X						
Brief Physical Exam[4]	X	X	X	X	X	X	X
Ambulatory/Movement Status[5]	X	X	X	X			
Height and Weight	X					X	X
Peak Temperature	X	X	X	X			
Prior and concomitant medications	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Record adjunctive therapeutic procedures (if performed i.e. Surgery)[6]		X					
Standard of Care Radiology Results	X						
Clinical outcome				X		X	X
AEs and SAEs	X	X	X	X	X	X	
CBC with differential [7]	X		X	X			
Chemistries (BUN, Creatinine, Alkaline Phosphatase, Bilirubin, AST, ALT) [7]	X		X	X			
CRP and ESR[8]	X	X	X	X	X	X	
Direct Coombs test	X			X			
Urine pregnancy test[9]	X					X	
CrCl calculation	X	If Clinically Indicated					
Standard of Care Blood Culture[10]		X					
Blood for PKanalyses[11]			X				
Standard of Care Purulent Material From Bone[12]	X						
Drug administration[13]		X	X	X	X		

Abbreviations: AE = adverse event; CBC = complete blood count; CrCl = creatinine clearance; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; SAE = serious adverse event.

1 Perform baseline assessments within 24 hours before first dose of IV study drug.
2 Interval history focusing on the use of the involved extremity. On Month 12 follow up interval problems such as pathologic fractures and growth disturbances will be evaluated only.
3 The presence of warmth, tenderness, swelling, erythema, and movement of the infected extremity will be recorded specifically. The circumference of the infected extremity taken at the location of point tenderness will be determined.
4 Involved extremity will be assessed as at enrollment, if possible. Most of the subjects are expected to have surgical incision and drainage procedures and thus assessing the extremity for swelling, erythema, warmth and tenderness may not be possible because of drains in place and large surgical dressings that cannot be removed.
5 The degree of the subject's ability to ambulate will be assessed if the osteomyelitis is in the lower extremity-i.e. walks unaided, able to bear weight, can walk aid using a walker, etc. The use of upper and lower extremities will be assessed in terms of movement and range of motion.
6 Any surgical procedures will be documented and the findings described.
7 CBC and chemistries . If not done for SOC, collect samples for research if clinically indicated.
8 CRP and ESR will be collected typically as part of standard of care. If not performed for SOC, collect samples for research if clinically indicated.
9 Perform test if subject is a female who has reached menarche. If a pregnancy test is positive post baseline, follow reporting requirements in Section 11.1.4.
10 Isolate susceptibilities will be performed on samples obtained from Pathology as per section 10.8.1.
11 Refer to section 10.9. PK samples may be collected 4 hours (+/- 30 minutes) after any infusion of ceftaroline fosamil (before the start of the next infusion) on days 2-5 and before oral switch.
12 If purulent material is being obtained from bone or subperiosteal abscesses at surgery or via drainage by interventional radiology, we will attempt to obtain specimens for measurement of ceftaroline concentrations.
13 Administer drug per Section 9.
14 Week 2 visit will occur only if the subject has been discharged prior to Week 2.

2. TABLE OF CONTENTS

3. LIST OF ABREVIATIONS AND DEFINITIONS OF TERMS

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
CA	Competent Authority
CABP	community-acquired bacterial pneumonia
CA-MRSA	community-acquired methicillin-resistant *Staphylococcus aureus*
CBC	complete blood count
CE	clinically evaluable
CFR	Code of Federal Regulations
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
C_{max}	maximum plasma drug concentration
CrCl	creatinine clearance
CRO	contract research organization
CRP	C-reactive protein
cSSSI	complicated skin and skin structure infection
CT	computed tomography
CXR	chest radiograph
CYP	cytochrome P450 enzyme
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOIV	End-of-Intravenous Study Drug
EOT	End-of-Therapy
FDA	US Food and Drug Administration
FLACC	Faces, Legs, Activity, Crying, and Consolability
FPS-R	Hicks Faces Pain Scale-Revised
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HA-MRSA	hospital-acquired methicillin-resistant *Staphylococcus aureus*
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ICF	informed consent form
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	intent to treat
IV	intravenous
LFU	Late Follow-up
MDRSP	multidrug-resistant *Streptococcus pneumoniae*
ME	microbiologically evaluable
MIC	minimum inhibitory concentration

MIC_{90}	minimum concentration required to inhibit the growth of 90% of organisms
MITT	modified intent-to-treat
mMITT	microbiological modified intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NOAEL	no-observable-adverse-effect level
OPAT	outpatient parenteral antimicrobial therapy
PBP	penicillin-binding protein
PCS	potentially clinically significant
PCV7	pneumococcal conjugate vaccine
PCV13	pneumococcal 13-valent conjugate vaccine
PD	pharmacodynamic
PISP	penicillin-intermediate *Streptococcus pneumoniae*
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PNSSP	penicillin-nonsusceptible *Streptococcus pneumoniae*
PO	by mouth (*per os*)
PRSP	penicillin-resistant *Streptococcus pneumoniae*
PVL	Panton-Valentine leukocidin
q6h	every 6 hours
q8h	every 8 hours
q12h	every 12 hours
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/2}$)
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	study day or standard deviation
TEAE	treatment-emergent adverse event
TOC	Test-of-Cure
ULN	upper limit of normal
US/USA	United States/United States of America
USP	United States Pharmacopeia
VATS	video-assisted thoracic surgery
VISA	vancomycin-intermediate *Staphylococcus aureus*
WBC	white blood cell

4. BACKROUND AND RATIONALE

4.1. Indication

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) isolates are now an important cause of systemic infections in children and has to be considered among the pathogens for any child presenting with a bone or joint infection depending on the local epidemiology. (1) (2) In Houston, TX CA-MRSA was the pathogen in 56 of 89 (63%) children with *S.aureus* osteomyelitis seen from August 2001 to July 2004.(3) In extending these findings, we found over the 10 year period from 2001 to 2010, 195 of 376 (52%) of *S. aureus* isolates from children with acute community acquired osteomyelitis were MRSA. In the United States and in a growing number of countries around the world, the USA300 clone is the most common or an emerging CA-MRSA pulsotype identified in invasive infections, including bone and joint infections.(4, 5)

Kingella kingae is a relatively common etiology of osteoarticular infection, primarily septic arthritis in children under 5 years of age.(6) The exact frequency of *K. kingae* bone and joint infections is difficult to determine because the organism is somewhat difficult to isolate using routine techniques. When polymerase chain reaction (PCR) techniques are applied to culture negative specimens from patients with presumed septic arthritis or acute osteomyelitis, *K. kingae* has been identified in a high percentage of cases for younger children.(7)

Streptococcus pneumoniae has been a relatively uncommon cause of bone and joint infections but does occur in children generally less than 24 months of age. Over a three-year period from September 1993 through August 1996, 42 children with pneumococcal bone or joint infections were identified at 8 children's hospitals.(8) In these same hospitals, 25 cases were identified over the three-year period 2007 through 2009. In 2010 and 2011, 2 and 4 cases occurred, respectively.(9) Thus, following the introduction of the 13-valent pneumococcal conjugate vaccine, pneumococcal bone and joint infection is likely to be even less common in young children.

In areas where CA-MRSA isolates account for $\geq$ 10% of community *S.aureus* isolates, an antibiotic effective against CA-MRSA isolates is recommended to be included in the initial empiric antibiotic regimen for treating children with suspected acute hematogenous osteomyelitis and/or septic arthritis.(10) Vancomycin is considered the antibiotic of first choice in the treatment of invasive CA- MRSA infections including musculoskeletal infections and is the agent to administer empirically for moderately to severely ill children. Nafcillin or oxacillin is also recommended along with vancomycin for severely ill children because these agents are superior to vancomycin for CA-MSSA bacteremic illness. Clindamycin is an option for empiric therapy in patients who are not very ill and in whom bacteremia is not suspected. Once an organism is isolated and antibiotic susceptibilities known, antibiotic therapy is modified. Clindamycin is an effective agent for clindamycin susceptible isolates.(11) Linezolid is quite active against CA-MRSA in vitro and can be administered orally with excellent bioavailability for treating CA-MRSA osteomyelitis in children and is considered an option, especially for clindamycin resistant isolates. Linezolid has been used most extensively for this indication in children in Taiwan where the CA- MRSA clone is typically resistant to clindamycin. (12) Daptomycin has been employed for treatment of osteomyelitis in adults but very little has been published regarding its use for this indication in children.(13) Trimethoprim-sulfamethoxazole may be very useful for treating acute osteomyelitis caused by *Kingella kingae* or in patients with culture-negative osteomyelitis in order to cover *K. kingae* and *S.aureus*.

Multiple studies have demonstrated that completing therapy with an oral agent following an initial duration of parenteral administration compared with parenteral therapy alone results in equivalent outcomes for treating musculoskeletal infections.(14, 15) In other studies, a high rate of complications was noted in children being treated for acute osteomyelitis who have parenteral antibiotics administered through a peripherally placed central catheter.(16) Thus, switching to oral administration of appropriate antibiotics to complete treatment of acute osteomyelitis is an important option for many, if not, most patients. The recommended duration of total treatment for acute osteomyelitis is at least three weeks depending on the clinical response of the patient.

4.2.Ceftaroline Fosamil

Ceftaroline is a fifth generation cephalosporin with excellent in vitro activity against *S. aureus* isolates including methicillin resistant strains.(17) Ceftaroline is approved by the United States Food and Drug Administration for treatment of skin and soft tissue infections caused by MRSA in adults based on two large randomized trials. (18, 19) In a rabbit model of MRSA osteomyelitis, ceftaroline and linezolid were significantly better than vancomycin in decreasing colony forming units in bone and joint fluid.(20) In seven of ten adult patients with deep seated MRSA infections, including osteomyelitis and septic arthritis in two patients each, ceftaroline treatment resulted in a microbiologic cure.(21) Clinical trials of ceftaroline in children are being conducted and the role of ceftaroline in treating MRSA osteomyelitis will need to be determined.

Seventeen clinical studies (3153 subjects in total) of ceftaroline fosamil have been conducted and completed to date. Eleven Phase 1 clinical pharmacology studies (305 subjects) have been completed, of which, 10 were conducted in adults. Two Phase 2 studies (242 subjects) were conducted in adult subjects with complicated skin and skin structure infection (cSSSI). Four Phase 3 studies (2606 subjects) have been completed. Studies P903-06 and P903-07 were conducted in adults with cSSSI (1378 subjects) and Studies P903-08 and P903-09 were conducted in adults with CAP (1228 subjects). The Phase 3 studies were multicenter, randomized, double-blind, comparative, safety and efficacy studies of ceftaroline fosamil (600 mg every 12 hours [q12h] as a 60-minute IV infusion; or 400 mg q12h if the subject had renal impairment) versus IV comparators. Studies P903-06 and P903-07 in cSSSI were identical in design. The comparator was vancomycin plus aztreonam (1 g of each q12h as 60-minute IV infusions with aztreonam discontinued if a gram-negative pathogen [infection] was not identified or suspected). The duration of ceftaroline fosamil or vancomycin (with or without aztreonam) administration was 5 to 14 days (with extensions allowed up to 21 days with previous approval of the Medical Monitor). Studies P903-08 and P903-09 were similar in design; the only difference was that a single day of adjunctive macrolide therapy (clarithromycin) was administered to subjects in both treatment groups in Study P903-08 and not in Study P903-09. The comparator was ceftriaxone (1 g q12h as a 30-minute IV infusion). The duration of ceftaroline fosamil or ceftriaxone administration was 5 to 7 days.

4.2.1. Summary of Toxicology Studies

Ceftaroline was well tolerated in various animal species in studies compliant with Good Laboratory Practices (GLP). When given as a single dose, ceftaroline fosamil had a minimum lethal dose > 2000 mg/kg in rats and monkeys. In repeat-dose studies (up to 13 weeks), the no-observable-adverse-effect level (NOAEL) was 30 mg/kg/day in rats and 32 mg/kg/day in monkeys. At high doses (270 mg/kg in rats and 64 mg/kg in monkeys), clinical signs or pathological observations (or both) revealed some treatment-related

abnormalities. The spleen and lymphoid organs (in 4-week studies only), and kidney were considered the potential targets for the toxicities of ceftaroline fosamil. These were typically reversible following a recovery period. Clonic/tonic convulsions were observed in rodents treated with high doses, similar to that observed following treatment with imipenem and other cephalosporins. No significant respiratory or cardiovascular toxicities were observed.

Reproductive toxicity, genotoxicity, and juvenile dose range-finding studies were also conducted with ceftaroline fosamil. There was no evidence of developmental toxicity in rats where the NOAEL was 300 mg/kg/day. In rabbits, the NOAEL was 100 mg/kg/day, and doses ≥ 50 mg/kg/day induced a statistically significant increase in the incidence of angulated hyoid alae, a common skeletal variation in this species.

Ceftaroline fosamil was not considered mutagenic and had minimal antigenic potential. It did not induce local irritation in rabbits and was compatible with human plasma.

A juvenile toxicity dose range-finding study was conducted with ceftaroline fosamil in rats. The NOAEL was 270 mg/kg, which represents a human exposure margin of 2 for ceftaroline (based on area under the plasma concentration versus time curve [AUC]).

From a preclinical perspective, ceftaroline fosamil has a comparable safety profile similar to other cephalosporins. The margins of exposure were 1 to 2 times the maximum recommended human dose.

4.2.2. Summary of Microbiological and Pharmacology Studies

Ceftaroline displays broad antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria. Like other β-lactams, ceftaroline is bactericidal and targets PBPs to inhibit bacterial cell wall biosynthesis. Ceftaroline binds with high affinity to PBPs from MSSA with additional ability to bind efficiently to PBP2a, the PBP present in MRSA responsible for methicillin resistance. Ceftaroline also retains activity against contemporary resistant organisms including both hospital-acquired methicillin- resistant S. aureus (HA-MRSA) and CA-MRSA, including S. aureus isolates resistant to clindamycin, in addition to vancomycin-intermediate S. aureus (VISA) and vancomycin-resistant S. aureus.

The minimum concentration required to inhibit the growth of 90% of organisms (MIC90) for S. aureus isolates is typically 1 mg/L (Study NSR-P903-M-071). Ceftaroline also has potent activity against isolates of streptococci, including Streptococcus viridans species, with MIC90 values typically < 0.12 mg/L. Erythromycin resistance in the streptococci has not been associated with increased MICs to ceftaroline.
Against the Enterobacteriaceae, MIC90 values for ceftazidime-susceptible isolates (ie, presumed non-extended-spectrum ß-lactamase-producing, non-AmpC β-lactamase-overexpressing) are typically ≤ 1 mg/L, as seen with Citrobacter freundii, Enterobacter cloacae, E. coli, K. pneumoniae, K. oxytoca, and Proteus mirabilis isolates. Ceftazidime-resistant strains had elevated MIC values to ceftaroline. Ceftaroline is less active against the indole-positive Proteae, including Morganella morganii and Providencia spp. (MIC90 > 32 mg/mL). Ceftaroline has little in vitro activity against Pseudomonas aeruginosa.

Resistance to ceftaroline develops at low frequency in vitro. For S. aureus, spontaneous resistant mutants to 4 times MIC of ceftaroline have not been observed (≤ 10-10). In various animal models of infection caused by either gram-positive or -negative bacteria, including MRSA and VISA, ceftaroline was shown to be highly effective.

In common with most β-lactams, free drug percentage of time above the minimum inhibitory concentration (%T > MIC) is the most appropriate parameter to predict efficacy of ceftaroline. The pharmacokinetic/pharmacodynamic (PK/PD) relationship for ceftaroline was initially evaluated in the murine neutropenic thigh infection model with several organisms including S. aureus (Andes and Craig, 2006). The mean free-drug %T > MIC required for stasis was 26% for S. aureus, regardless of the resistance phenotype.

The efficacy of ceftaroline against aerobic gram-positive and gram-negative microorganisms has been established in a variety of animal models of infection, including mouse peritonitis, sepsis, thigh infection, and pneumonia; and in rabbit models of endocarditis, pneumonia, osteomyelitis and meningitis. In the mouse pneumonia model, the efficacy of ceftaroline fosamil was compared with that of vancomycin and linezolid (Study TAK-599/00063). The activity of ceftaroline against MRSA was better than that of vancomycin and linezolid in a neutropenic murine pneumonia model in which 20 mg/kg doses of each drug were administered subcutaneously three times daily for
2 days beginning 1 day after intranasal inoculation. Ceftaroline reduced viable bacterial counts in infected lungs by 4 log units compared to the untreated control ($p < 0.01$), while both vancomycin and linezolid failed to reduce the bacterial counts. When the study was performed by administering the first dose only 2 hours after inoculation, all 3 drugs exhibited bactericidal activity, perhaps because the bacteriostatic agents, vancomycin and linezolid, were only effective during the early stage of infection when the bacterial counts were low, while ceftaroline, being bactericidal, was active even later during the infection.

A dose-fractionation study (P903-M-097) was conducted in a neutropenic murine lung infection model using various clinical isolates of S. aureus isolates (MSSA and MRSA, with ceftaroline MICs ranging from 0.5 to 4 mg/L) to define the required magnitude of ceftaroline exposure (ie, free drug concentration above the MIC [f T > MIC]) that reliably results in efficacy. Additionally, the efficacy of a human simulated regimen of ceftaroline 600 mg every 12 hours (q12h) administered as a 1-hour intravenous (IV) infusion was evaluated.

Bronchopulmonary penetration of ceftaroline was also assessed in the murine pneumonia model by collecting epithelial lining fluid (ELF) via bronchoalveolar lavage (BAL) at various time points after dosing in both infected and uninfected animals. Ceftaroline concentrations in the ELF of infected, neutropenic mice were nearly the same as their corresponding serum concentrations. Therefore, f T > MIC exposures in ELF were similar to what was seen in the serum and the penetration ratio for ceftaroline into mouse ELF based on area under the plasma concentration versus time curve (AUC) was approximately 100%. The ceftaroline f T > MIC values in serum associated with stasis and a 1-log10 CFU reduction in bacterial density were 16.5% and 41.4%, respectively. The human simulated 600 mg q12h dose regimen provided considerable decreases in bacterial densities for all the S. aureus isolates tested, which had ceftaroline MICs of 0.5 to 4

mg/L. In a rabbit model of pneumonia, dose administration was by a computer-controlled infusion pump to accurately simulate human PK for ceftaroline and comparator ceftriaxone (Croisier-Bertin et al, 2011). Three pneumococcal isolates with varying susceptibility to penicillin were evaluated, including penicillin-susceptible S. pneumoniae (PSSP), penicillin-intermediate S. pneumoniae (PISP), and penicillin-resistant S. pneumoniae (PRSP). Human simulated dosing (600 mg every q12h for ceftaroline, 1 g every 24 hours [q24h] for ceftriaxone) was administered for 2 days beginning 5 hours after endobronchial challenge with 5×109 colony forming units (CFU). Ceftaroline and ceftriaxone were similarly effective in reducing bacterial burden in the lungs (approximately 7 log CFU/g, to essentially undetectable levels) for the PSSP and PISP infections, but only ceftaroline was bactericidal against the PRSP isolate. A second study evaluated efficacy against a PVL-producing isolate of USA300 MRSA in the same rabbit pneumonia model with simulated human dosing for ceftaroline, vancomycin, linezolid, and clindamycin (Croisier-Bertin et al, 2011). High mortality observed in untreated control animals was completely prevented by ceftaroline and also greatly reduced by linezolid and clindamycin, while animals treated with vancomycin showed only marginal improvement in survival. Bacterial counts in lung were lowest in the ceftaroline-treated animals (approximately 5-log reduction compared to control), although not statistically different from the animals receiving linezolid, lindamycin, or vancomycin. PVL toxin levels were monitored and treatment with clindamycin, ceftaroline, and linezolid were found to result in greatly reduced levels of toxin compared to vancomycin, which may partially explain the enhanced tissue damage observed in lungs of vancomycin- treated animals.

The plasma protein binding of ceftaroline in vitro was generally low (mean ± SD of 20% ± 6.1%) and concentration independent in human plasma over the clinically relevant concentration range. In vitro oxidative metabolic studies with liver microsomes demonstrated that the metabolism of ceftaroline is not dependent upon cytochrome P450 enzymes (CYP). In vitro studies in human liver microsomes indicated that neither ceftaroline fosamil nor ceftaroline inhibits the major CYP isoenzymes. In addition, studies in human hepatocytes also demonstrated that ceftaroline fosamil, ceftaroline, and ceftaroline M-1 are not inducers of CYP activity. Therefore, ceftaroline is not expected to inhibit or induce the clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

No differences in the pharmacokinetics of ceftaroline fosamil, ceftaroline, or ceftaroline M-1 were noted between genders in rats and monkeys. In addition, there was no accumulation of ceftaroline fosamil or ceftaroline after repeated once-daily administration, and only moderate accumulation of ceftaroline M-1 was observed in the repeat-dose toxicology studies.

Safety pharmacology studies were performed in various experimental animal models and in vitro testing systems to examine the effects of ceftaroline fosamil on behavioral and physiological effects, respiratory function, and the cardiovascular system.

4.2.3. Completed Pediatric Studies

One of the 11 Phase 1 clinical pharmacology studies, Study P903-15 “Pharmacokinetics of a Single Dose of Ceftaroline in Subjects 12 to 17 Years of Age Receiving Antibiotic Therapy,” was conducted in adolescents.

Study P903-15 was a Phase 1, multicenter, open-label, noncomparative, single-dose study of ceftaroline fosamil in subjects 12 to 17 years of age, inclusive, who were hospitalized and receiving antibiotic therapy for treatment of infections of any type. Subjects received a single IV infusion of ceftaroline fosamil at a dose of 8 mg/kg if weighing < 75 kg (165.4 lb) or 600 mg if weighing 75 kg (165.4 lb) or more. The primary objective was to evaluate the single-dose pharmacokinetics of ceftaroline, the prodrug ceftaroline fosamil, and the inactive M-1 metabolite. The secondary objective was to evaluate the safety of ceftaroline in adolescent subjects.

Nine subjects, 5 male and 4 female subjects with a mean age of 13.7 years (range 12 to 16 years), were enrolled in the study. One subject was prematurely discontinued from study drug due to infusion site extravasation that was moderate in severity and assessed by the Investigator as unrelated to ceftaroline. This subject received approximately 80% of the planned dose.

The remaining 8 subjects each received a complete dose of ceftaroline fosamil. All subjects completed the study and were included in the Safety Population. Eight treatment-emergent adverse events (TEAEs) occurred in 5 subjects. All TEAEs were mild or moderate in severity. Three TEAEs (extrasystoles, vomiting, and "electrocardiogram [ECG] prolonged QT interval") were considered related to ceftaroline by the Investigator and each occurred in a different subject. All TEAEs resolved except for "ECG prolonged QT interval" in 1 subject that was detected on Study Day 2 and was not assessed further. (The subject's QTcB and QTcF values were < 450 msec and similar between the predose and postdose measurements.) One subject mentioned above prematurely discontinued study drug, but no subjects prematurely withdrew from the study or died. One subject with osteomyelitis had a serious adverse event (SAE) of a pathologic fracture of the humerus that occurred 13 days after infusion of ceftaroline fosamil. The fracture was mild in severity and considered by the Investigator as unrelated to ceftaroline.

No clinical chemistry or urinalysis values met potentially clinically significant (PCS) criteria. One hematology value met PCS criteria, one subject who had received several blood replacement products for blood loss secondary to trauma and surgery had a high activated partial thromboplastin time. One subject met PCS criteria for a vital sign value, a low diastolic blood pressure. Neither PCS value was associated with a TEAE. No ECG parameter values met PCS criteria. Most abnormal laboratory, vital sign, and ECG findings were consistent with the subjects' medical conditions.
These results show that a single dose of ceftaroline fosamil (8 mg/kg up to a maximum dose of 600 mg, IV) was generally well tolerated by 9 adolescent subjects who were hospitalized and receiving antibiotic therapy for an infection of any type. The mean values of maximum plasma drug concentration (Cmax) and AUC for ceftaroline observed in adolescent subjects (12 to 17 years) who received ceftaroline fosamil at a dose of 8 mg/kg (600 mg for subjects weighing > 75 kg) were approximately 10% and 23%, respectively, less than the values observed in adult subjects following administration of a 600-mg dose of ceftaroline fosamil.

Study P903-21 "Pharmacokinetics of a Single Dose of Ceftaroline fosamil in Children Ages Birth to Younger than 12 Years With Suspected or Confirmed Infection" was a Phase 1, multicenter, open-label,

sequential, single-dose, prospective study of ceftaroline fosamil. Subjects were enrolled in 5 sequential cohorts of descending age; enrollment of sequential cohorts could overlap, depending on results from intermittent PK analyses. Subjects who were hospitalized and receiving antibiotic therapy for treatment of suspected or confirmed infections were enrolled and each received a single dose of IV ceftaroline fosamil.

Data from Study P903-21, Study P903-15, and other data were used to determine the ceftaroline fosamil dose in this study.

4.2.4. Summary of Studies in Adults

In single- and multiple-dose Phase 1 studies in adults, the Cmax and AUC of ceftaroline increased approximately in proportion to increases in dose within the dose range of 50 to 1000 mg, and no accumulation of ceftaroline fosamil or active ceftaroline was observed with either q12h or every 24-hour multiple dose regimens. Ceftaroline Cmax was generally reached near the end of the IV infusion, and the terminal elimination half-life (T½) of ceftaroline was typically in the range of 2.0 to 2.6 hours. Following IV infusion of [14C] ceftaroline fosamil, 87.5% of the dose of radioactivity was excreted in urine and 6.0% was excreted in feces, confirming that urinary excretion is the principal route of elimination. A significant percentage of the ceftaroline fosamil dose was excreted in the urine as ceftaroline (approximately 40% to 70%). No dosage adjustment is considered necessary for subjects with mild renal impairment. Dosage adjustment is recommended in subjects with moderate and severe renal impairment (creatinine clearance [CrCl] ≤ 50 mL/min).

Study CEF-PK-02 was a recently completed Phase 1, open-label, multiple-dose study in healthy adult subjects to assess the concentration of ceftaroline in ELF. Subjects were randomized to receive one of the following dosing regimens: Treatment A - 600 mg ceftaroline fosamil q12h for 3 days with a single dose on Day 4; Treatment B - 600 mg ceftaroline fosamil every 8 hours (q8h) for 3 days with a single dose on Day 4. Twenty-five subjects received each dosing regimen. Plasma samples for PK analysis were collected p r e d o s e and over 24 hours after the final dose on Day 4. Subjects underwent bronchoscopy and BAL at a single time point after the last dose in order to collect ELF. Preliminary data indicate that the ratio of AUCs of free ceftaroline in ELF to free ceftaroline in plasma, assuming 20% protein binding in plasma and no protein binding in ELF, was approximately 22%. All subjects had measurable ceftaroline concentrations in ELF at 1, 2, 4, and 6 hours after the start of the ceftaroline fosamil infusion. Eight out of 10 subjects that underwent BAL 8 hours after dosing had measurable ceftaroline concentration in ELF, and none of the 5 subjects that underwent BAL at 12 hours after dosing had measurable ceftaroline in ELF. These data demonstrate that ceftaroline is able to penetrate into ELF and concentrations of ceftaroline in ELF appreciably exceeded the MIC90 for ceftaroline against S. aureus (1 mg/L) at 1 and 2 hours after the start of the ceftaroline fosamil infusion in all subjects. Plasma and ELF concentrations were similar for the 2 dosing regimens, with the q8h regimen showing slightly (approximately 15% to 20%) higher concentrations on average. Ceftaroline appeared to be eliminated from plasma and ELF at a similar rate.

Ceftaroline fosamil at a dose of 600 mg (or 400 mg if the subject had renal impairment) q12h was well tolerated in 693 adult subjects in the 2 completed Phase 3 CAP studies. As shown in these studies,

monotherapy with ceftaroline fosamil at a dose of 600 mg administered as a 1-hour IV infusion q12h for 5 to 7 days is effective for the treatment of CABP caused by susceptible isolates of the following gram- positive and gram-negative microorganisms: S. pneumoniae (including cases with concurrent bacteremia), MSSA, H. influenzae, K. pneumoniae, K. oxytoca, and E. coli.

Therapy with ceftaroline fosamil was shown to be noninferior to ceftriaxone (with or without clarithromycin) in the clinical cure rate at TOC in the 2 coprimary populations (Modified Intent-to-Treat Efficacy and Clinically Evaluable [CE]). Noninferiority was also demonstrated in the clinical response at End-of-Therapy (EOT) in the 2 coprimary populations. Finally, efficacy results consistently demonstrated similar cure rates between ceftaroline and ceftriaxone in important subgroups and key secondary analyses. Clinical response rates at Study Day 4 in these two studies were 69.6% and 69.0% for ceftaroline versus 58.3% and 61.4% for ceftriaxone.

4.3.Rationale for Present Study

Ceftaroline has excellent in vitro activity against *S.aureus* including MRSA, Group A streptococcus, *Streptococuccus pneumoniae* and *Kingella kingae* which are the most common causes of acute hematogenous osteomyelitis in children. Ceftaroline is now approved by the FDA for treating children with community-acccquired pneumonia and skin and soft tissue infections, conditions which are generally caused by the same bacteria that cause hematogenous osteomyelitis. Currently CA-MRSA is a major problem throughout the United States and the use of vancomycin or clindamycin has increased dramatically in children as a result.

Dosing of vancomycin is problematic and vancomycin has common side effects such as red man syndrome and renal dysfunction. Clindamycin is not recommended if there are concerns for concomitant bacteremia because it is a bacteristatic agent. Daptomycin may be useful but is just being studied in pediatric patients for osteomyelitis and should not be used if there is evidence of concomitant pneumonia. Thus, the addition of another parenteral antibiotic for treatment of acute hematogenous osteomyelitis in children is desirable.

There is no safety data available for administering ceftaroline to adults every 8 hours. The safety data for administering ceftaroline every 8 hours to children has been determined in three pediatric trials. (Cannavino et al. A Randomized, Prospective Study of Pediatric Patients with Community-acquired Pneumonia Treated with Ceftaroline Versus Ceftriaxone. Pediatr Infect Dis J 2016; 35:752-9; Blumer et al. A Multicenter, Randomized, Observer-blinded, Active-Controlled Study Evaluating the Safety and Effectiveness of Ceftaroline Compared with Ceftriaxone Plus Vancomycin in Pediatric Patients with Complicated Community-acquired Bacterial Pneumonia. Pediatr Infect Dis J 2016; 35:760-6; Korczowski et al. A Multicenter, Randomized, Observer-blinded, Active-controlled Study to Evaluate the Safety and Efficacy of Ceftaroline Versus Comparator in Pediatric Patients with Acute Bacterial Skin and Skin Structure Infection. Pediatr Infect Dis J 20; 35:e239-47. The most common adverse events for patients receiving ceftaroline were diarrhea and vomiting. Eosinophilia developed in about 5% of patients. The proportions of patients developing adverse events were similar for the

ceftaroline and comparator groups in each of these studies. We are using the same dose and interval for ceftaroline that was used for the pediatric trial of ceftaroline for complicated pneumonia (clinical trials identifier number NCT01669980).

4.4. Rationale for Ceftaroline Fosamil Dosage Regimen

The selected ceftaroline dose regimens (15 mg/kg [600 mg if > 40 kg] as a 2-hour infusion q8h) are expected to achieve PK/PD targets associated with 1-log kill of S. aureus in the murine pneumonia model for organisms with MIC values up to 1 mg/L in > 90% of patients 2 months to < 18 years. The median Cmax value in children 1 year to < 18 years with normal renal function dosed with 15 mg/kg q8h as a 2-hour infusion predicted to be less than the median Cmax value in adults dosed with 600 mg q8h as a 1-hour infusion. The median AUC0-24h in children 1 year to < 18 years dosed with the above regimen is predicted to be up to 15% greater than in adults dosed with 600 mg q8h. The median f T > MIC for an MIC of 1 mg/L is predicted to be 84-93% for the recommended pediatric dose regimens compared to 100% in adults dosed with 600 mg q8h.

Initially, the sponsor believed that a dose of15 mg/kg q8h to match the dose of 600 mg q8h in adults was appropriate for children from 6 months to <18 years. However, based on findings in the pediatric ABSSSI and CABP studies, a lower dose of 10 mg/kg q8h is more appropriate for children from 6 months to < 2 years in order to avoid higher AUC values. The 10 mg/kg q8h dose in this age range is expected to result in a median fT (unbound drug time over MIC)>MIC of 78-88% for an MIC of 1 mg/L and 58-66% for an MIC of 2 mg/L. This would give nearly 100% target attainment for a target of 50% at an MIC of 1 mg/L. The higher dose of 15 mg/kg q8h would still be appropriate for children 2 and older.

4.5. Outpatient Parenteral Antimicrobial Therapy

If a subject is going to require continued parenteral therapy with an antibiotic to complete therapy at home, they will be dropped from the study protocol because of the difficulty in providing parenteral antibiotics in a study using a home health company. Patient will continue therapy with another agent at home. The subjects will be followed and assessed for outcome at the time of discharge as well as for safety assessments at the completion of ceftaroline administration. The home therapy will be determined as clinically indicated for such subjects.

4.6. Oral Drugs

A switch to one of the following open-label PO drugs (as per accepted clinical care processes) is expected / allowed on or after EOIV assessments are completed and if criteria in Section 9.2 are met:

- PO clindamycin 13 mg/kg/dose q8h in subjects with proven MRSA infection due to clindamycin susceptible MRSA or if no pathogen has been isolated.

OR

- PO cephalexin 25 to 33 mg/kg/dose q 8 hours in subjects with proven MSSA infection.

OR

- PO linezolid 600 mg q12h (Children ≥ 12 years old) or 10 mg/kg q8h (children < 12 years old) in

subjects with clindamycin-resistant MRSA pathogens or for subjects with MRSA isolates who are unable to tolerate clindamycin.

5. STUDY OBJECTIVES

5.1. Primary Objectives

- Evaluate the safety of ceftaroline in pediatric subjects 1 to 17 years of age (inclusive) with acute hematogenous osteomyelitis at the end of intravenous therapy.

5.2. Secondary Objectives

- Evaluate efficacy of ceftaroline in pediatric subjects with acute hematogenous osteomyelitis at the end of IV therapy, at the end of total therapy (anticipated to be at 4 to 6 weeks after enrollment), and at one year after enrollment.
- Evaluate clearance of *S. aureus* bacteremia if blood cultures initially positive.
- Assess proportion of patients with plasma levels of ceftaroline that exceed 1 µg/mL for over 60% of a dosing interval.

6. STUDY DESIGN

This is a Phase 1/2, open-label, single-center study to determine safety and tolerability of ceftaroline in pediatric subjects 1 to 17 years of age (inclusive) with signs and symptoms of acute hematogenous osteomyelitis at the end of intravenous therapy. After informed consent/assent is obtained, ceftaroline will be administered intravenously. After the subject has been afebrile for at least 48 hours, has negative blood cultures, is clearly improving in general, is able to eat and drink, and is able to use or move the involved extremity, the subject may be switched to oral antibiotic administration as outlined in section 5.4.2. The expenses will be covered by the study.

6.1. Outcome Measures

Primary: Safety evaluations will be conducted in the children who have started treatment with ceftaroline. Assessments will include:

- AEs, SAEs, deaths, and discontinuations due to SAEs.
- Vital signs and laboratory parameters.

Secondary:

- Clinical response (the subject has been afebrile for at least 48 hours, has negative blood cultures, is clearly improving in general, is able to eat and drink, and is able to use or move the involved extremity) at the end of parenteral therapy (approximately days 5 to 14) by subject and by baseline pathogens although *S.aureus* is expected to be the predominant pathogen.
- Clinical outcome (site of infection has complete resolution of pain, swelling and warmth and the patient is able to use the affected extremity normally and is back to normal activities) at the EOT and at the one year follow up visit.

- Clinical relapse within a year of enrollment in the study or the development of a pathologic fracture.

PK:

- Concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma.
- If available, concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in purulent material such as bone or subperiosteal abscess or synovial fluid.

6.2. Number of Subjects

18 Children 1 to 17 years of age, inclusive. Each subject will receive ceftaroline. 2 subjects above 5 years old will be enrolled before the younger subjects are enrolled.

Based on A'Hern's single-stage design for Phase II clinical trials 18 subjects would be required to reject $H_0:\pi \leq 0.50$ and conclude $H_1:\pi \geq 0.80$ with 80% power assuming a Type 1 error rate of 0.05.

6.3. Expected Duration of Subject Participation

The duration of subject participation from signing the informed consent form will be up to 14 months (includes screening period (1 Day), study IV drug administration (approximately 5-14 Days), Standard of Care Oral Drug Administration (4-5 weeks) (**the total maximum treatment period is typically 6 weeks**), and a follow-up visit 12 months after the last dose of study drug). Baseline assessments for study eligibility will occur within 24 hours before the first dose of study drug. A minimum of 2 days (48 hours) of study drug administration is required.

6.4. Data Review Committee

A Data and Safety Review Committee (DRC) will be established to review safety data on a regular basis to ensure safety of all subjects enrolled.

A DRC 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 DRC 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 enrollment.

A detailed DRC charter will be prepared by the Investigator and agreed to by all DRC members before initiation of enrollment in this study. This charter will document the timing, membership, analysis content, and review procedures for each DRC meeting. Safety information will be prepared in advance of each DRC meeting. Safety analyses will include, at a minimum, summaries of study disposition and all SAEs, deaths, and discontinuations due to AEs, PCS laboratory results, and individual subject listings of selected safety data.

7. SELECTION, DISCONTINUATION AND WITHDRAWAL OF STUDY SUBJECTS

7.1. Inclusion Criteria

Subjects are required to meet the following inclusion criteria:

1. Informed consent in writing from parent(s) or other legally acceptable representative(s) and assent from subject (if appropriate according to local requirements).
2. Male or female 1 to 17 years of age, inclusive.
3. Suspected hematogenous SA osteomyelitis in a large bone (upper or lower extremities, pelvis) based on clinical findings and radiology results.
4. One to three sites of osteomyelitis with expectation that transition to oral antibiotics will be likely prior to discharge to complete IV therapy (The second or third site might be contiguous like a proximal tibia and distal femur but could also be at sites unrelated such as a distal femur and pelvic bone).
5. Female subjects who have reached menarche must have a negative urine pregnancy test.
6. Female subjects who have reached menarche and are sexually active must be willing to practice sexual abstinence or dual methods of birth control (eg, condom or diaphragm with spermicidal foam or gel) during treatment and for at least 28 days after the last dose of any study drug.
7. Sufficient IV access to receive medication.

7.2. Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria. Septic arthritis contiguous to the site of osteomyelitis is not an exclusion criterion.

1. Received more than 24 hours of IV antibiotics prior to enrollment.
2. More than three bones infected.
3. Disseminated infection or is admitted to the pediatric intensive care unit.
4. Underlying condition (excludes mild eczema or reactive airways disease).
5. Suspected venous thrombosis or concern for endocarditis.
6. Requirement for other reasons for another antibiotic potentially active against organisms commonly causing osteomyelitis in children.
7. Creatinine clearance < 50 mL/min/1.73m^2 (calculated by the Schwartz formula)
8. AST or ALT > 3 times the upper limit of normal.
9. Neutropenia (<500 neutrophils/mm^3)
10. Thrombocytopenia (<50,000 platelets/mm^3)
11. Females who are currently pregnant or breast feeding.
12. Hypersensitivity reaction to any Beta-lactam antibiotic
13. Has had an allergic reaction to ceftaroline in the past.

7.3. Prior and Concomitant Treatment and Medications

All antimicrobials, pain medications, and antipyretics that were taken or received within 14 days before the first dose of study drug and those taken during the study will be recorded. Pain medications such as acetaminophen-codeine, ketorolac, and morphine, will be recorded unless they were used during administration of anesthesia. Medications related to adverse events will be recorded. In addition, each subject's history of pneumococcal vaccinations will be documented, if possible.

7.4. Permitted Treatment and Medications

Concomitant use of the following is permitted: 1) antipyretics as standard of care for fever or symptoms, provided temperature is measured before administration of the antipyretics; 2) Topical antibiotics; and 3) all other concomitant medications and nutrients necessary for the health and well- being of the subject.

7.5. Prohibited Medications and Therapies

Concomitant use of the following is not permitted: 1) potentially effective systemic antibacterial therapy; 2) any drug known to exhibit a contraindicated drug-drug interaction with the study drug; or labeled contraindication to use of oral drug(s); and 3) other cephalosporins/aminoglycosides or other nephrotoxic agents.

7.6. Screening Failures

Subjects who sign and date the ICF but who fail to meet the inclusion and exclusion criteria are defined as screen failures. A screening log will be maintained for all screen failures.

7.7. Subject Discontinuation or Withdrawal

Subjects should be encouraged to complete all study outcome assessments. However, a subject may be discontinued from study drug or may withdraw assent/consent to participate in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled. Subjects will be assessed for safety of ceftaroline at the time points outlined in the schedule of evaluations, if possible.

7.7.1. Off Study Criteria:

- Subjects who require continued home parenteral antibiotics will be discontinued from the study.
- Subjects that require IV treatment after switching to Oral drug.
- If a subject's estimated CrCl decreases to < 50 mL/min during the treatment period, the subject will be discontinued from the study.
- Diarrhea (the occurrence of > 4 loose stools /day) with blood or mucus
- Moderate to severe maculopapular rash that does not resolve following administration of diphenhydramine (Benadryl®) or any urticarial rash.
- Absolute neutrophil count < 500 WBC/mm^3 (Grade 4)
- Hemolytic anemia Grade 2 (evidence of > 2 g decrease in hemoglobin but does not require blood transfusion) or above.
- Thrombocytopenia-Platelet count < 100,000/mm^3 (Grade 1)
- AST/ALT > 3 X ULN (grade 3)

7.8. Premature Discontinuation From Study Drug Administration

7.8.1. Discontinuations Due to Safety

Assessments and Procedures: A subject who is prematurely discontinued from study drug administration (ie, before the anticipated full course of study drug required for effective treatment of hematogenous SA osteomyelitis *for safety reasons)* should have EOIV or EOT (if on PO drug) assessments conducted per Section 9, and undergo subsequent assessments at FU, if possible. The same procedures will be followed if the subject needs to continue home IV therapy to complete treatment because the subject is intolerant of an appropriate oral antibiotic or there is no oral agent that is active against the organism isolated.

Clinical Outcome Assessment:

If a subject prematurely discontinues the study drug due to an SAE and requires alternative non-study antimicrobials for hematogenous SA osteomyelitis, the subject should be assessed indeterminate.

Reasons: Reason(s) for premature discontinuation from study drug administration *due to safety* may include, but are not limited to, the following:

- Occurrence of an SAE that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from the study drug or oral drug administration.

- Known pregnancy or breastfeeding during the drug administration period. A female subject whose pregnancy test is positive at the end of total treatment must be followed through the immediate postnatal period or until termination of the pregnancy. Every pregnancy will be reported as soon as possible (within 24 hours of learning of the pregnancy), as described in Section 11.1.4.

7.8.2. Discontinuations Due to Insufficient Therapeutic Effect

Assessments and Procedures: A subject who is prematurely discontinued from study drug administration *due to insufficient therapeutic effect* should have EOIV (if on IV study drug) or EOT (if on PO drug) assessments conducted per Section 9, and undergo subsequent safety assessments at the 4 to 6 week follow up visit. If a subject is discontinued from IV study drug administration *due to insufficient therapeutic effect* and is switched to an alternative IV antibiotic, the alternative therapy should be recorded.

Clinical Outcome Assessment: A subject who is prematurely discontinued from study drug administration *due to insufficient therapeutic effect* should be assessed as a clinical failure on the day of discontinuation. Such a subject will be automatically assigned an outcome of clinical failure at all subsequent evaluation time points.

Reasons: Reason(s) for discontinuation from study drug administration *due to insufficient therapeutic effect* may include, but are not limited to, the following:

- Clinical Worsening: A subject who shows signs of clinical worsening may be prematurely discontinued from study drug administration at any time. If the Investigator deems the benefit-to-risk ratio of continuing study drug acceptable, study drug administration for at least 48 hours is encouraged before discontinuation. If the subject is improving clinically but the blood cultures are persistently positive for *S. aureus* for up to 5 days, ceftaroline can be continued at the discretion of the investigator.

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

7.8.3. Withdrawal

Assessments and Procedures: A subject may withdraw from the study, or be withdrawn at the request of their parent(s) or legally acceptable representative(s), the Investigator, or Sponsor. A subject who is withdrawn completely from this study during study treatment should be encouraged to undergo, if possible, EOIV (if on IV study drug) or EOT (if not on IV study drug) assessments per Section 10, respectively, on the day of withdrawal.

Clinical Outcome Assessment: A subject withdrawn from the study who is not assessed as a clinical failure should be assessed as indeterminate at all subsequent outcome evaluation time points.

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

- Withdrawal of assent or consent
- Lost to follow up
- Significant subject noncompliance, defined as refusal or inability to adhere to the prescribed dosing or

follow-up regimen
- Investigator determination that it is in the best interest of the subject to withdraw from the study, due to reasons other than an SAE.

7.9. Replacement of Subjects

Subjects who are withdrawn from study before receiving any amount of study drug will be replaced in order to enroll a total of 18 treated subjects for safety evaluations. Subject numbers will not be reused.

7.10. Stopping Rules

The incidence or severity of AEs indicates a potential health hazard to subjects. The study will be stopped if treatment failures occur in two patients or severe adverse events that are due to ceftaroline in the opinion of the PI occur in two patients.

8. STUDY DRUGS

8.1. Ceftaroline Fosamil Intravenous Study Drug

Ceftaroline fosamil for injection, 400 or 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 pH of the constituted solution between 4.8 and 6.5.

Ceftaroline fosamil is approved in the United States for use in adults with ABSSSI or CABP. Ceftaroline fosamil is limited in pediatric subjects to investigational use only. Refer to the current ceftaroline fosamil IB (Ceftaroline fosamil, 2011) for additional information.

Dosing Information: IV ceftaroline fosamil **15 mg/kg** (or 600 mg if > 40 kg) infused over 120 (± 10) minutes q8h (± 1 hour) for children **2 years of age – 17 years** of age (inclusive).

IV ceftaroline fosamil **10 mg/kg** infused over 120 (± 10) minutes q 8h (± 1 hour) for children from 1 **year of age to < 2 years** (inclusive).

8.2. 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.

8.3. Storage

Vials containing unconstituted ceftaroline fosamil are stored according to labeled requirements.

8.4. Criteria for Switching to Oral Drug

A switch to PO drug (see Section 9.2.2) is allowed on or after EOIV assessments are completed and if all of the following criteria are met:

- Received at least 48 hours of IV study drug.

- Clinical signs and symptoms have been assessed.
- Ability to maintain oral intake.
- Afebrile (temperature ≤ 38.0°C) for at least 48 hours.
- Blood cultures are negative for 48 hours.
- CRP decreased compared with baseline value.
- Absence of new or improvement in at least 1 of the following signs and symptoms and worsening of none:
  - Extremity movement or pain.
  - Able to ambulate either unaided or with a walker or crutches.

Subjects that require IV treatment after switching to Oral drug will be discontinued from the study.

8.4.1. Oral Drug Options

The appropriate PO drug may depend on the pathogen, the options include the following:

- Preferred oral switch for subjects with infections due to methicillin-susceptible *S. aureus*, Group A streptococcus or *K. kingae*-cephalexin 75-100 mg/kg/day in three divided doses.
- Alternative PO option for subjects with proven MRSA infections due to clindamycin-susceptible is clindamycin 13 mg/kg/dose q8h. Clindamycin is also the oral agent typically selected to complete treatment when no organism is isolated.
- Linezolid is an option for completing therapy for a clindamycin resistant MRSA isolate or for patients who cannot tolerate clindamycin. Linezolid dosing is 10 mg/kg/dose q 8 hours for children ≤ 12 year old and 600 mg q 12 hours for children > 12 years old.

Dosing adjustments are discussed in Section 9.3. Consult the package inserts, labels, and local dosing guidelines regarding preparation, storage, administration, maximum doses, contraindications, warnings, precautions, and AEs reported with the use of the PO study drugs.

8.5. Dose Adjustments

Subjects with moderately (CrCl 30 mL/min to ≤ 50 mL/min) or severely (CrCl < 30 mL/min) impaired renal function (calculated using the appropriate updated Schwartz "bedside" formula; Schwartz et al, 2009) will not be enrolled in this study; thus no ceftaroline fosamil dose adjustments are expected to be required for renal impairment. However, if the subject's estimated CrCl decreases to < 50 mL/min during the treatment period, the patient will be discontinued from the study.

8.6. Adjunctive Surgical Procedures

Details of adjunctive surgical procedure(s) related to hematogenous SA osteomyelitis that are performed for any subject in this study will be collected and documented.

8.7. Treatment Compliance

Treatment compliance will be documented in the eCRF by recording the date, time, and whether or not each IV dose study drug was completely infused and, if applicable, whether or not each intended dose of PO drug was taken.

8.8. Accountability Procedures

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.

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.

All study drugs provided by Allergan should be retained at the site until otherwise instructed in writing by Allegan. Upon completion of the study all used (vials), unused, and partially used IV study drugs will be shipped to a site designated by Allergan. Refer to the Pharmacy instructions or package insert for additional information.

9. STUDY ASSESSMENTS AND PROCEDURES

The Schedule of Assessments and Procedures is located in Table 2.1. Unless otherwise noted, the assessments and procedures should be conducted in person by the Investigator or designee.

Any protocol-required evaluations (eg, laboratory tests and) already done locally on the corresponding study day, including baseline, as part of the subject's regular medical care can be recorded on the eCRFs and do not have to be repeated for purposes of this study.

9.1. Baseline

Baseline procedures must be completed within 24 hours before the start of the first dose of IV study drug. Potential subjects who do not meet entrance criteria may, as appropriate, repeat baseline evaluations at a later time for possible enrollment into the study.

- Obtain informed consent in writing from parent(s) or legally acceptable representative(s) and assent from subject (as applicable) before initiating any study assessment or procedure.
- Collect demographic information including age, gender, race and ethnicity.
- Clinical Assessments (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):
    - Obtain a complete medical and surgical history, including history of surgical procedures for complications of hematogenous SA osteomyelitis (eg, drainage of the bone) and all active conditions and all conditions diagnosed within the previous 5 years (from the following categories: allergic; cardiovascular; dermatological; gastrointestinal; genital and reproductive; head, eyes, ears, nose, and throat; hematology; hepatic; immunological; metabolic and endocrine; musculoskeletal;

neurologic; psychiatric; renal; and respiratory).

- Record prior medications (Section 8.3) taken or received within 14 days before the first dose of study drug. For children who are being breast fed, record all medications taken by the lactating mother during the 3 days before the first dose of IV study drug. In addition, record history of pneumococcal vaccinations.

- Record standard of care radiology results.
- Record the findings of a complete physical examination including physical findings of hematogenous SA osteomyelitis (eg, warmth, tenderness, swelling, erythema, and movement of the infected extremity). Involved extremity will be assessed as at enrollment, if possible. Most of the subjects are expected to have surgical incision and drainage procedures and thus assessing the extremity for swelling, erythema, warmth and tenderness may not be possible because of drains in place and large surgical dressings that cannot be removed.

- Record height and weight.

- Record vital signs: resting pulse, blood pressure, and respiratory rate; and highest daily temperature (Tmax) measured.

- Identify, assess, and record any AEs and SAEs starting from the time that informed consent is obtained.

- Record adjunctive therapeutic procedures (eg, surgeries).

Laboratory Assessments (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated)

- Any protocol-required eligibility laboratory evaluations already done locally as part of the subject's regular medical care within 24 hours before the start of the first dose of IV study drug do not have to be repeated for purposes of this study.

- Collect complete blood count (CBC) with differential and CRP, ESR, BUN, and Creatinine lab results.

- Blood cultures per standard of care.

- Obtain blood samples for Alkaline Phosphatase, Bilirubin, AST and ALT.

- Obtain blood sample for Direct Coombs test.

- Obtain urine sample for pregnancy test (for a female who has reached menarche); ensure that the test is negative before enrollment.

- Estimate CrCl using the updated Schwartz "bedside" formula (Schwartz et al, 2009):

  $$\text{CrCl (mL/min/1.73m}^2\text{)} = \frac{0.413 \times \text{height (length) (cm)}}{\text{serum creatinine (mg/dL)}}$$

- Collect purulent material from bone only if a procedure is performed for standard of care.

- Enroll subject after verifying that the subject meets all study inclusion and no exclusion criteria. There

should be no medically inappropriate delay in enrollment and subsequent administration of IV study drug.

9.2.Study Day 1

- Study Drug Administration:

IV ceftaroline fosamil **15 mg/kg** (or 600 mg if > 40 kg) infused over 120 (± 10) minutes q8h (± 1 hour) for children **2 years of age – 17 years** of age (inclusive).

IV ceftaroline fosamil **10 mg/kg** infused over 120 (± 10) minutes q 8h (± 1 hour) for children from **1 year of age to < 2 years** (inclusive).

The following Clinical and Laboratory Assessments for Study Day 1 do not need to be repeated if dosing of study medicine is done on the same day as the baseline visit:

- Clinical Assessments - after at least 1 dose of IV study drug (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):
    - Record concomitant medications (Section 8.3). For subjects who are being breast fed, record all medications taken by the lactating mother.
    - Record resting vital signs (pulse, blood pressure, and respiratory rate), and highest postdose temperature measured.
    - Record adjunctive therapeutic procedures (eg, surgeries).
    - Record standard of care radiology results.
    - Evaluate and record physical findings of hematogenous SA osteomyelitis (eg, warmth, tenderness, swelling, erythema, and movement of the infected extremity). Most of the subjects are expected to have surgical incision and drainage procedures and thus assessing the extremity for swelling, erythema, warmth and tenderness may not be possible because of drains in place and large surgical dressings that cannot be removed. The degree of the subject's ability to ambulate will be assessed if the osteomyelitis is in the lower extremity-i.e. walks unaided, able to bear weight, can walk aid using a walker, etc. The use of upper and lower extremities will be assessed in terms of movement and range of motion.
    - Identify, assess, and record any new or ongoing AEs or SAEs
- Laboratory Assessments - after at least 1 dose of IV study drug (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated)
    - If clinically indicated, calculate CrCl using the updated Schwartz "bedside" formula (Schwartz et al, 2009).
    - Collect results of blood cultures only if conducted per standard of care.
    - Collect purulent material from bone only if a procedure is performed for standard of care.

9.3.Study Days 2-14

The total duration of IV ceftaroline is dependent on the subject's response to therapy but 5-14 days is anticipated in most subjects. If the subject is able to switch to oral drug before Day 15, the procedures outlined for Day 15 (EOIV) should be performed. The rest of the visit schedule will be followed as described in Table 2.1.

- Study Drug Administration:

IV ceftaroline fosamil **15 mg/kg** (or 600 mg if > 40 kg) infused over 120 (± 10) minutes q8h (± 1 hour) for children **2 years of age – 17 years** of age (inclusive).

IV ceftaroline fosamil **10 mg/kg** infused over 120 (± 10) minutes q 8h (± 1 hour) for children from **1 year of age to < 2 years** (inclusive) until the subject transitions to oral therapy.

- Clinical Assessments – any time during study day (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):
  - Record concomitant medications (Section 8.3). For subjects who are being breast fed, record all medications taken by the lactating mother.
  - Record resting vital signs (pulse, blood pressure, and respiratory rate), and highest postdose temperature measured.
  - Record adjunctive therapeutic procedures (eg, surgeries).
  - Record standard of care radiology results.
  - Evaluate and record physical findings of hematogenous SA osteomyelitis (eg, warmth, tenderness, swelling, erythema, and movement of the infected extremity). Most of the subjects are expected to have surgical incision and drainage procedures and thus assessing the extremity for swelling, erythema, warmth and tenderness may not be possible because of drains in place and large surgical dressings that cannot be removed. The degree of the subject's ability to ambulate will be assessed if the osteomyelitis is in the lower extremity-ie. walks unaided, able to bear weight, can walk aid using a walker, etc. The use of upper and lower extremities will be assessed in terms of movement and range of motion.
  - Identify, assess, and record any new or ongoing AEs or SAEs
- Laboratory Assessments – any time during the study period if clinically indicated (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):
  - Collect CRP and ESR lab results, if clinically indicated.
  - Collect CBC with differential, BUN, and Creatinine, lab results, if clinically indicated.
  - Obtain blood sample for Alkaline Phosphatase, Bilirubin, AST and ALT, if clinically indicated.
  - If clinically indicated, estimate CrCl using the updated Schwartz "bedside" formula (Schwartz et al, 2009).
  - Collect results of blood cultures only if conducted per standard of care.

- Collect purulent material from bone only if a procedure is performed for standard of care when possible.

- PK Procedures:

  - Efforts will be made to obtain 1 PK blood sample (approximately 0.6 mL) at steady state from all subjects who received ceftaroline fosamil on Days 2 to 5 of treatment (only one PK sample collected on days 2-5) 4 hours (+/- 30 minutes) after the end of the infusion (before the start of the next infusion). PK samples may be collected after any infusion of ceftaroline fosamil on those days and before oral switch.

  - If purulent material is being obtained from bone or subperiosteal abscesses at surgery or via drainage by interventional radiology, we will attempt to obtain specimens for measurement of ceftaroline concentrations.

9.4.Study Day 15 (End of IV Treatment-EOIV)

The total duration of IV ceftaroline is dependent on the subject's response to therapy but 5-14 days is anticipated in most subjects. If the subject is able to switch to oral drug before Day 15, these procedures may be performed before Day 15. Conduct EOIV assessments within 24 hours after administration of the last dose of IV study drug (subjects will likely remain in the hospital for less than 24 hours once they are transitioned to oral therapy as per standard of care) or at time of premature discontinuation of study drug or early withdrawal from study (if on IV study drug). Conduct the EOIV assessments in place of the regular study visit assessments that would have been performed the day of that visit. A subject may be eligible to switch to PO drug on or after Study Day 3 (Section 9.2). EOIV assessments must occur before starting PO drug. The rest of the visit schedule should be followed as described in Table 2.1.

If applicable, as IV study drug may or may not be given on the same calendar day as EOIV assessments, administer IV study drug IV ceftaroline fosamil **15 mg/kg** (or 600 mg if > 40 kg) infused over 120 (± 10) minutes q8h (± 1 hour) for children **2 years of age – 17 years** of age (inclusive).

IV ceftaroline fosamil **10 mg/kg** infused over 120 (± 10) minutes q 8h (± 1 hour) for children from **1 year of age to < 2 years** (inclusive) until the subject transitions to oral therapy.

- Clinical Assessments - any time during study day, but before starting PO study drug, if applicable (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):

  - Record concomitant medications (Section 8.3). For subjects who are being breast fed, record all medications taken by the lactating mother.

  - Record vital signs: resting pulse, blood pressure, and respiratory rate; and highest daily temperature measured.

  - Record adjunctive therapeutic procedures (eg, surgeries).

  - Record standard of care radiology results.

  - Evaluate and record physical findings of hematogenous SA osteomyelitis (eg, warmth, tenderness, swelling, erythema, and movement of the infected extremity). Most of the subjects are expected

to have surgical incision and drainage procedures and thus assessing the extremity for swelling, erythema, warmth and tenderness may not be possible because of drains in place and large surgical dressings that cannot be removed. The degree of the subject's ability to ambulate will be assessed if the osteomyelitis is in the lower extremity-ie. Walks unaided, able to bear weight, can walk aid using a walker, etc. The use of upper and lower extremities will be assessed in terms of movement and range of motion.

- Assess clinical outcome (site of infection has complete resolution of pain, swelling and warmth and the patient is able to use the affected extremity normally and is back to normal activities).
- Identify, assess, and record any new or ongoing AEs or SAEs. Subjects will likely remain in the hospital for less than 24 hours once they are transitioned to oral therapy as per standard of care.

- Laboratory Assessments- any time during study day, but before starting PO drug, if applicable. If these assessments are performed within 48 hours of latest results, do not repeat these assessments (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):
  - Collect CRP and ESR lab results.
  - Collect CBC with differential, BUN, and Creatinine.
  - Obtain blood sample for AST, ALT, Alkaline Phosphatase, Bilirubin and Direct Coombs.
  - If clinically indicated, estimate CrCl using the updated Schwartz "bedside" formula (Schwartz et al, 2009).
  - Collect results of blood cultures for *S. aureus* only if conducted per standard of care.
  - Collect purulent material from bone only if a procedure is performed for standard of care when possible.

9.5. Week 2, Week 4, and Week 6 After Discharge

- PO drug administration:
  - PO clindamycin 13 mg/kg/dose q8h in subjects with proven MRSA infection due to clindamycin susceptible MRSA or when no pathogen is isolated.
    OR
  - PO cephalexin 25 to 33 mg/kg/dose q 8 hours in subjects with proven MSSA infection.
    OR
  - PO linezolid 600 mg q12h (Children > 12 years old) or 10 mg/kg q8h (children ≤ 12 years old) in subjects with clindamycin-resistant MRSA pathogens.

Clinical Assessments - any time during study day (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):

- Obtain an interval medical and surgical history focusing on the involved extremity, including history

of surgical procedures for complications of hematogenous SA osteomyelitis (eg, drainage of the bone) and all active conditions from the following categories.

- Record concomitant medications (Section 8.3). For subjects who are being breast fed, record all medications taken by the lactating mother.

- Record vital signs: resting pulse, blood pressure, and respiratory rate.

- Record adjunctive therapeutic procedures (eg, surgeries).

- Record standard of care radiology results.

- Evaluate and record physical findings of hematogenous SA osteomyelitis (eg, warmth, tenderness, swelling, erythema, and movement of the infected extremity). Most of the subjects are expected to have surgical incision and drainage procedures and thus assessing the extremity for swelling, erythema, warmth and tenderness may not be possible because of drains in place and large surgical dressings that cannot be removed. The degree of the subject's ability to ambulate will be assessed if the osteomyelitis is in the lower extremity-ie. walks unaided, able to bear weight, can walk aid using a walker, etc. The use of upper and lower extremities will be assessed in terms of movement and range of motion.

- Assess clinical outcome (site of infection has complete resolution of pain, swelling and warmth and the patient is able to use the affected extremity normally and is back to normal activities).

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

Laboratory Assessments - any time during study day, but before starting PO study drug, if applicable (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):

- Collect CRP and ESR lab results, if clinically indicated for standard of care.

- If clinically indicated, estimate CrCl using the updated Schwartz "bedside" formula (Schwartz et al, 2009).

9.6. End of Antibiotic Therapy (EOT)/Week 4/ OR Week 6

Note that EOT visit and assessments may occur at the Week 4 visit or the Week 6 visit. If the EOT visit occurs on the same day as the Week 4 or Week 6 visit, only the EOT visit will be recorded in CTMS.

- If applicable, as PO drug may or may not be given on the same calendar day as EOT assessments, administer PO drug as described in Section 9.2.

- Clinical Assessments - any time during visit (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):

- Record concomitant medications (Section 8.3). For subjects who are being breast fed, record all medications taken by the lactating mother.
- Record height and weight.
- Record vital signs: resting pulse, blood pressure, respiratory rate and temperature.
- Record adjunctive therapeutic procedures (eg, surgeries), if performed.
- Record standard of care radiology results.
- Evaluate and record physical findings of hematogenous SA osteomyelitis (eg, warmth, tenderness, swelling, erythema, and movement of the infected extremity). The degree of the subject's ability to ambulate will be assessed if the osteomyelitis is in the lower extremity-ie. walks unaided, able to bear weight, can walk aid using a walker, etc. The use of upper and lower extremities will be assessed in terms of movement and range of motion.
- Assess clinical outcome (site of infection has complete resolution of pain, swelling and warmth and the patient is able to use the affected extremity normally and is back to normal activities).
- Identify, assess, and record any new or ongoing AEs or SAEs

- Laboratory Assessments (Local Laboratory) - any time during visit, Collect CRP and ESR lab results, if clinically indicated for standard of care.
  - Obtain urine sample for urine pregnancy (for a female who has reached menarche).
  - If clinically indicated, estimate CrCl using the updated Schwartz "bedside" formula (Schwartz et al, 2009).

9.7. Follow Up

Conduct FU assessments 12 months after administration of the last dose of the drug (IV or PO whichever is the latest).

- Clinical Assessments - any time during visit (assessments will be performed for research unless they are already being performed per standard of care; exceptions are indicated):
  - Record concomitant medications (Section 8.3). For subjects who are being breast fed, record all medications taken by the lactating mother.
  - Record vital signs: resting pulse, blood pressure, respiratory rate and temperature.
  - Record adjunctive therapeutic procedures (eg, surgeries).
  - Record standard of care radiology results.
  - Assess clinical outcome (site of infection has complete resolution of pain, swelling and warmth and the patient is able to use the affected extremity normally and is back to normal activities).
  - Identify, assess, and record event such as pathologic fractures and growth disturbances.
  - Laboratory Assessments - any time during visit:

- o If clinically indicated, estimate CrCl using the updated Schwartz "bedside" formula (Schwartz et al, 2009).

9.8. Safety Lab Tests

9.8.1. Study Required Lab Tests

Alkaline Phosphatase, Bilirubin, AST, ALT and Direct Coombs (DATscreen) will be obtained within 24 hours prior to enrollment; and at the completion of ceftaroline treatment (EOIV visit).

Isolate susceptibilities: The ceftaroline MIC of S. aureus isolates or other isolates such as Group A streptococcus, *Streptococcus pneumoniae* or *Kingella kingae* that are obtained from the patients with acute hematogenous osteomyelitis will be determined using Clinical and Laboratory Standards Institute (CLSI) methods. These will be performed in the CAP certified Infectious Disease Research Laboratory. CLSI interpretive breakpoints will be used to determine if the isolate is susceptible, intermediate or resistant to ceftaroline. The samples will be obtained from pathology (from already collected samples) to conduct the Isolate susceptibility studies.

9.8.2. Standard of Care Labs

Record the following local safety labs if performed per standard of care: hemoglobin, hematocrit, WBC, platelet count, BUN, serum creatinine, CRP and ESR. If multiple laboratory tests are obtained on the same day, record test results closest to administration of study drug.

9.8.3. PK Assessments

The pharmacokinetic (PK) outcome measures will include concentrations of ceftaroline, ceftaroline fosamil (prodrug), and ceftaroline M-1 (inactive metabolite) in plasma in subjects on days 2 to 5 of treatment (only one PK sample collected on days 2-5) 4 hours (+/- 30 minutes) after the end of the infusion (before the start of the next infusion). Efforts will be made to obtain 1 PK blood sample (approximately 0.6 mL) at steady state from all subjects who receive ceftaroline fosamil. PK samples may be collected after any infusion of ceftaroline fosamil on those days and before oral switch.

If purulent material is being obtained from bone or sub periosteal abscesses at surgery or via drainage by interventional radiology, we will attempt to obtain specimens for measurement of ceftaroline concentrations.

All samples will be sent to Keystone Bioanalytical, Inc. for analysis.

9.9. Diagnostic Imaging and Non-Pharmacological Assessments

All diagnostic imaging procedures including x-ray or MRIs, in accordance with routine standard of care, will be recorded on the study eCRF. Non-pharmacologic treatments/procedures (such as surgeries) performed in accordance with routine standard of care will be recorded on the study eCRF.

10. SAFETY ASSESSMENTS

Subjects must be seen by a physician or an appropriately trained healthcare professional at every study visit, and the evaluation must be documented. The procedures discussed below will be completed at the designated visits as outlined in Section 10.0.

10.1. Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of AEs are as follows:

- Changes in the general condition of the subject.
- Subjective symptoms offered by or elicited from the subject.
- Objective signs observed by the Investigator or other study personnel.
- All diseases that occur after the start of the study, including any change in severity or frequency of preexisting disease.
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study.

10.2. Causality and Severity Assessments

The causality assessment must be recorded on the appropriate AE CRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the study drug caused the event?

Yes: There is evidence to suggest a causal relationship between the study drug and AE, ie,:

- There is a reasonable temporal relationship between the study drug and the event, and
- The event is unlikely to be attributed to underlying/concurrent disease, other drugs, or other factors, and/or
- Positive de-challenge and/or re-challenge exist

No: There is no evidence to suggest a causal relationship between the study drug and AE, ie,:

- There is no reasonable temporal relationship between the study drug and the event, or
- The subject did not take the study drug, or

- The event is likely to be attributed to underlying/concurrent disease, other drugs, or other factors, or

- The event is commonly occurring in the (study) population independent of drug exposure

The Investigator must provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE screen(s) of the subject's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a subject outcome or AE-required treatment measure associated with a threat to life or functionality (Section 11.1.2). Severity will be assessed according to the following scale.

Mild:	Minor awareness of signs or symptoms that are easily tolerated without specific medical intervention.
Moderate:	Discomfort that interferes with usual activities and may require minimal intervention.
Severe:	Significant signs or symptoms that are incapacitating with an inability to work or perform routine activities and/or that require medical intervention.

10.3. Serious Adverse Events/Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Results in a life threatening adverse event
- 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 anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the

current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Emergency room visits that do not result in hospitalization (ie, an overnight stay) should be evaluated for one of the other serious outcomes to determine if they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for preexisting conditions that did not worsen) are excluded from SAE reporting.

Study endpoints (eg, mortality or major morbidity) must be reported to FDA by the Sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of the CFR § 312.32. However, if a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the drug and the event (eg, death from anaphylaxis), the event must be reported under CFR § 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

The new regulations require that “study endpoints (eg, mortality or major morbidity) must be reported according to the protocol instead of as IND safety reports except when there is evidence suggesting a causal relationship between the drug and the event.”

Any worsening of hematogenous SA osteomyelitis under study because of lack of therapeutic effect of any study drug (reported within study endpoints reporting time frame) is captured as an efficacy endpoint and is, therefore, excluded from SAE reporting, unless the event is considered related to the drug.

10.4. Follow Up of Serious Adverse Events

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. The investigator will follow all SAEs until resolution, stabilization, or the event is otherwise explained. DRC will follow all SAEs until resolution, stabilization, until otherwise explained, or until the last patient completes the final follow-up, whichever occurs first.

10.5. Collecting and Reporting Adverse Events and Serious Adverse Events

Research related AEs and SAEs are collected from the signing of the informed consent form (ICF) (and assent form, if applicable) until EOT. At Month 12 follow up problems such as pathologic fractures and growth disturbances will be evaluated. The investigational site personnel are to follow unresolved AEs and SAEs at EOT until resolution or stabilization.

At each visit, subjects and/or their parent(s) (or other legally acceptable representative[s]) are to be queried regarding any new or ongoing AEs/SAEs that have occurred since the previous visit. Each, as appropriate, will be asked to volunteer information with a non-leading question such as, for the subjects, “How have you felt since your last visit?” Study center personnel will then record all pertinent information on the appropriate screens of the subject’s eCRF.

All research related AEs/SAEs reported by the subject or subject's parent(s) (or legally acceptable representative[s]) or observed or otherwise identified by the Investigator (or other study site personnel) at a defined study visit or during any communication with the subject (or subject's representative[s]) occurring outside a defined study visit must be documented.

All research related AEs must be recorded on the appropriate CRF, whether or not they are considered causally related to the study drug.

For every AE, the Investigator must:

- Provide an assessment of the severity, causal relationship to the study drug), and seriousness of the event (ie, SAE).
- Document all actions taken with regard to the study drug.
- Detail any other treatment measures taken for the AE.

Within 24 business hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to Allergan on an SAE/AESI form (Global Patient Safety & Epidemiology Form) and to the FDA and IRB per regulation/local IRB policy.

If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The PI will transmit the SAE/AESI Form to the email and fax number indicated on the most current version of the form. Even if an initial report is made by telephone, an SAE/AESI form completed with all available details must still be emailed/faxed within 24 business hours of knowledge of the event at the study center.

Supplemental information shall be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE/AE. Any medications or procedures necessary for treatment of the SAE/AE must be recorded on the appropriate screen(s) of the subject's CRF. All SAEs/AEs are to be followed until resolution or until the SAE/AE is deemed stable. The Sponsor may contact the study center to solicit additional information or follow up on the event.

10.6. Other Reportable Events – Pregnancy

Study center personnel must report every pregnancy on a Clinical Trial Pregnancy Form as soon as possible (within 24 business hours of learning of the pregnancy) to the email/fax number as indicated on the form, even if no AE has occurred. Pregnancies in female partners of male subjects must also be reported. The pregnancy must be followed to term and the outcome reported by completing the Clinical Trial Pregnancy Form. If, however, the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), in addition to the Clinical Trial Pregnancy Form, a separate SAE/AESI Form for Clinical Trials must be filed as described in Section 11.1.3 with the appropriate serious criterion (eg, hospitalization) indicated on the SAE/AESI Form.

10.7. IND Safety Reports

For serious adverse events that require expedited regulatory reporting under 21 CFR 312.32(c)(1), the PI will notify the FDA in a written Investigational New Drug (IND) safety report and report to the IRB per local

policy.

10.8. Other Clinical Assessments

Safety parameters will be monitored according to standard medical practice and guidelines for IV administration of study drug. Vital sign assessments (pulse, blood pressure, respiratory rate, and temperature) will be conducted at the specified time points outlined in the Schedule of Assessments and Procedures (Table 2-1) and Section 10.0.

Medical and surgical history, prior and concomitant medications, height (length), weight, physical examination findings, and hematogenous SA osteomyelitis sign and symptom assessments will be recordedat baseline and if applicable, during study according to the Schedule of Assessments and Procedures (Table 2–1) and Section 10.0.

10.9. Laboratory Assessments

Blood samples for clinical laboratory tests and urine samples for pregnancy tests (females who have reached menarche only) will be collected at baseline and throughout the study according to the Schedule of Assessments and Procedures (Table 2–1) and Section 10.0. If a subject's estimated CrCl (as calculated using the updated Schwartz "bedside" formula; Schwartz et al, 2009) decreases to < 50 mL/min during the treatment period, the DRC should be contacted. If a subject's hemoglobin or hematocrit decreases significantly (Investigator's judgment) during IV study drug therapy, an evaluation for hemolytic anemia will be conducted per standard of care.

11. DATA MANAGEMENT

An institutional Electronic Data Capture (EDC) system, the Clinical Trials Management System (CTMS), will be used for this trial. Study specific electronic case report forms (eCRFs) designed to provide reliable and secure data entry for clinical research purposes will be utilized. The web based software tools in the CTMS employ 2048-bit Secure Socket Layer (SSL) encryption; all transactions are encrypted in both directions.
The CTMS meets the regulatory requirements of HIPAA and 21 CFR Part 11 compliance. In addition, the system has an offsite, fully mirrored disaster recovery backup.

Data entered into the CTMS will include a subject study identification number; names will not be linked with subject data in the database. Study staff will maintain records linking the subject name with the identification number assigned for the study in a secure area.

All data changes in the CTMS are written to an audit trail that identifies the user, date and time, as well as the old value and new value. Both patient-related data as well as trial configuration data are written to the audit trail. Data are saved at regular intervals during data entry to prevent loss of information in the event of a disruption of the Internet connection.

The eCRFs include standard logical checks and range checks, as well as support for multiple languages in the user interface. There is emphasis on tracking deadlines and milestones with automated notifications and reports of study progress. The module includes a data locking mechanism to ensure that data accuracy and integrity are maintained to facilitate data analyses promptly after study completion.
Several levels of security are employed to ensure privacy and integrity of the study data, including the following:

- Study access requires use of assigned unique user names and passwords that are modified at specified time intervals

- Individual roles and access levels are assigned
- Passwords are changed regularly
- Data are not stored on laptop computers

The study coordinator will be responsible for data entry and maintaining appropriate source documentation. Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data.
The study coordinator will enter data within 7 days of the screening visit and within 14 days of each subsequent visit.

12. STATISTICAL ASSUMPTIONS

12.1. Statistical Methods and Planned Analysis

- Descriptive statistical methods will be used to summarize the demographic characteristics of the subjects as well as selected clinical features such as duration of fever or positive blood cultures, time until normalization of ESR and CRP.
- The proportion of children with plasma concentrations of ceftaroline that exceed 1µg/mL at 5-6 hours following a 2 hour infusion of ceftaroline dose will be determined.
- Safety analyses will be conducted on all subjects who received at least one dose of ceftaroline.

12.2. Primary End Points

- Assessment of safety of ceftaroline in children during initial treatment of acute hematogenous osteomyelitis at the end of intravenous therapy.

12.3. Secondary Endpoints

1. Successful treatment of acute hematogenous osteomyelitis at one year after completion of a 4 to 6 week total antibiotic treatment and at one year after enrollment.

2. Clearance of *S. aureus* bacteremia if blood cultures initially positive.

3. The proportion of children with plasma concentrations of ceftaroline that exceed 1µg/mL for over 60% of a dosing interval.

12.4. Safety Analysis

Adverse event and serious adverse event monitoring, vital signs and laboratory tests (CBC,BUN, Creatinine, Bilirubin, Alkaline Phosphatase, AST and ALT will be obtained within 24 hours prior to enrollment and weekly during ceftaroline treatment and at the completion of ceftaroline treatment). The Alkaline Phosphatase, Bilirubin, AST/ALT results may not be available prior to enrollment of the patient.
We do not anticipate that the AST/ALT concentrations will be > 3 UNL but if they were to be this elevated, the patient subject will be dropped from the study immediately.

Safety parameters include AEs, SAEs, deaths, clinical laboratory parameters (eg, hematology parameters, chemistry parameters), and vital signs. For each safety parameter, the last assessment made before the first dose of IV study drug will be used as the baseline for all analyses.

The incidences of TEAEs, 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 the study drug, 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 PCS laboratory results will be summarized.

12.5. Efficacy Analysis

- Clinical response by subject and by baseline pathogen at the conclusion of IV ceftaroline.
- Clinical outcome at the completion of total therapy (IV plus oral)
- Clinical outcome at one year after enrollment into study long-term follow-up.

12.6. Interim Analysis

An interim analysis of pharmacokinetics parameters may be performed using data from the first 5 evaluable patients to complete the study. The results of this interim analysis may be used to confirm the planned Ceftaroline dose, or support an appropriate dose adjustment. Enrollment will not be held during the interim PK analysis.

12.7. PK Analysis

The mean and median concentrations of ceftaroline in plasma at the end of infusion will be determined. The proportion of children with plasma ceftaroline concentrations $\geq$ 1 µg/mL at 4 hours after infusion will be determined.

The plasma levels of ceftaroline obtained at 4 hours after the end of a 2 hour infusion will be compared to the ceftaroline MIC for the S. aureus isolate recovered causing the osteomyelitis. Ideally, the plasma level should exceed the MIC at this time point which would be for at least 75% of a dosing interval. Assuming the patients do well clinically, there will be no adjustment of the dose even if the target concentration is not achieved at the 6 hour time point following the start of ceftaroline infusion. However, if two subjects do not improve as anticipated, the study will be halted and plasma levels compared to the MICs of the causative S. aureus isolates. If plasma levels exceed the MIC and yet the subjects are considered treatment failures in that they are not responded as expected, the investigator would conclude that ceftaroline may not be particularly effective in treating S. aureus osteomyelitis in children. If the plasma levels at this time point are below the MIC, a dose modification may be considered but the investigator may decide that studying ceftaroline for this indication is no longer necessary.

12.8. Handling of Dropouts and Missing Data

Every effort will be made to collect all data at specified times. All subjects and data will be assessed up to the time that the subject is dropped. Missing data will be noted in the CRFs.

13. ADMINISTRATIVE ASPECTS

13.1. Compliance with Regulatory Requirements

This study will be conducted in compliance with the current ICH E6 GCP, the ethical principles of the Declaration of Helsinki, current FDA GCP guidelines, and any additional national or IRB -required procedures, whichever represents the greater protection for the individual.

13.2. Institutional Review Board

The IRB must approve the protocol or amended protocol (if applicable) and the corresponding ICF (and assent form, if applicable) before the study may be initiated and/or amendments are instituted (unless required for subject safety); and any recruiting materials before use.

The Investigator is responsible for informing the IRB of any changes made to the protocol, and to advise the IRB, at least once a year, about the progress of the study. The Investigator is also responsible for notifying the IRB of any significant AEs that occur during the study according to local IRB requirements.

13.3. 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). For a child to participate in the study, the child's parent(s) or legally authorized representative(s) will sign and date the ICF at the first visit, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits, before initiation of any study-related procedures. A pediatric subject who is old enough to provide assent, will be asked for such assent, according to institution-specific guidelines. A copy of the signed ICF (and assent form, if applicable), must be provided to the subject's parent(s) or legally acceptable representative(s). If applicable, the ICF (and assent form, if applicable) will be provided in certified translation for non-English-speaking subjects and parents or other legally acceptable representatives. Signed ICFs (and assent form, if applicable) will remain in the subjects' study files and be available for verification at any time.

13.4. Confidentiality

Personal study patient data collected and processed for the purposes of this study will be managed by the investigator and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Monitors, auditors and other authorized agents of Cempra Pharmaceuticals, the IRB approving this research, and the FDA, as well as any other applicable regulatory authorities, will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patients, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the patient identities will remain confidential.

13.5. Compensation, Insurance, and Indemnity

Information regarding compensation, insurance, and indemnity is presented in the clinical trial research agreement.

13.6. Protocol Amendments

If a protocol has been filed with regulatory agencies or submitted to an IRB and requires changes, a protocol amendment will be written. Any changes to the protocol will be made by the Investigator. Changes to the protocol will be submitted to regulatory agencies when required.

13.7. Case Report Forms

An institutional Electronic Data Capture (EDC) system, the Clinical Trials Management System (CTMS), will

be used for this trial. Study specific electronic case report forms (eCRFs) designed to provide reliable and secure data entry for clinical research purposes will be utilized. The web based software tools in the CTMS employ 2048-bit Secure Socket Layer (SSL) encryption; all transactions are encrypted in both directions. The CTMS meets the regulatory requirements of HIPAA and 21 CFR Part 11 compliance. In addition, the system has an offsite, fully mirrored disaster recovery backup.

Data entered into the CTMS will include a subject identifiers and study identification number; the subject identifiers other that the study identification will not be included in the database reports when required. All data changes in the CTMS are written to an audit trail that identifies the user, date and time, as well as the old value and new value. Both patient-related data as well as trial configuration data are written to the audit trail. Data are saved at regular intervals during data entry to prevent loss of information in the event of a disruption of the Internet connection.

The eCRFs include standard logical checks and range checks, as well as support for multiple languages in the user interface. There is emphasis on tracking deadlines and milestones with automated notifications and reports of study progress. The module includes a data locking mechanism to ensure that data accuracy and integrity are maintained to facilitate data analyses promptly after study completion.
Several levels of security are employed to ensure privacy and integrity of the study data, including the following:

- Study access requires use of assigned unique user names and passwords that are modified at specified time intervals
- Individual roles and access levels are assigned
- Passwords are changed regularly
- Data are not stored on laptop computers

The study coordinator will be responsible for data entry and maintaining appropriate source documentation. Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data.
The study coordinator will enter data within 7 days of the screening visit and within 14 days of each subsequent visit.

13.8. Source Document Maintenance

Source documents may include, but are not limited to, study progress notes, study- or subject-specific e-mail correspondence, computer printouts, laboratory data, and recorded data from automated instruments. The original signed ICF (and assent form, if applicable) for each participating subject 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 inspections.

13.9. Study Monitoring/Quality Assurance

The study data will be reviewed by the Investigator and the QA Analyst as per the internal institutional SOPs.

The Investigator will allow the applicable regulatory authorities to inspect facilities and records relevant to this study.

13.10. Study File Management

The study file will contain all required documents as per the regulations, IRB requirements and the internal SOPs including, but not be limited to:

- Final study protocol.
- Protocol amendments (if applicable).
- Study manual (if applicable).
- ICF and assent (blank).
- Revised ICFs and/or all addenda (blank).
- Copy of signed form(s) Form FDA 1572.
- Curricula vitae of investigator and sub investigators.
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions.
- Annual IRB updates and approvals.
- All correspondence between the investigator, IRB, Allergan and FDA.
- Copies of all IND safety reports submitted to the FDA and IRB correspondence documenting their submission (if applicable).
- Laboratory certifications/normal laboratory value ranges.
- Screening log.
- Study drug accountability records and invoices for receipt/return of study drug.
- Protocol signature page.
- Laboratory director's curriculum vitae and medical/professional license, if available.

13.11. Study Completion

The following data and materials will be on file before a study can be considered completed or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period.
- eCRFs properly completed by appropriate study personnel and electronically signed and dated by the investigator.
- Complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material).
- Copies of protocol amendments and IRB approval/notification, if appropriate.
- A summary of the study prepared by the principal investigator (an IRB summary letter is acceptable).

13.12. Audits

During the course of the study, or after completion of the study, FDA and/or other regulatory authorities may audit the study. Every attempt will be made to notify Allergan in writing in advance of the audit.

13.13. Retention of Records

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

Records and documents pertaining to the conduct of this study in all formats (including, but not limited to, written, electronic, magnetic, and x-rays) must be retained by the Investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. These records include eCRFs, source documents, ICFs (and assent form, if applicable), regulatory documents, clinical reports and laboratory results (including, but not limited to, all local and central laboratory results),

and medication inventory records.

After the required retention period, long-term storage arrangements will be made for such study records if possible.

If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party.

At the request of a subject's parent(s) (or other legally authorized representative[s]), medical information may be given to the subject's personal physician or other appropriate medical personnel responsible for the subject's welfare.

13.14. Publication Policy

The data generated in this clinical study are the exclusive property of the Investigator and are confidential. The Investigator will make all reasonable efforts to publish the results of the study in an appropriate peer-reviewed journal.

14. REFERENCES

1. Arnold SR, Elias D, Buckingham SC, Thomas ED, Novais E, Arkader A, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant Staphylococcus aureus. J Pediatr Orthop 2006;26(6):703-8.
2. Saavedra-Lozano J, Mejias A, Ahmad N, Peromingo E, Ardura MI, Guillen S, et al. Changing trends in acute osteomyelitis in children: impact of methicillin-resistant Staphylococcus aureus infections. J Pediatr Orthop 2008;28(5):569-75.
3. Bocchini CE, Hulten KG, Mason EO, Jr., Gonzalez BE, Hammerman WA, Kaplan SL. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous *Staphylococcus aureus* osteomyelitis in children. Pediatrics 2006;117(2):433-440.
4. David MZ, Daum RS. Community-associated methicillin-resistant Staphylococcus aureus: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev 2010;23(3):616-87.
5. Nimmo GR. USA300 abroad: global spread of a virulent strain of community-associated methicillin-resistant Staphylococcus aureus. Clin Microbiol Infect 2012.
6. Yagupsky P, Porsch E, St Geme JW, 3rd. Kingella kingae: an emerging pathogen in young children. Pediatrics 2011;127(3):557-65.
7. Verdier I, Gayet-Ageron A, Ploton C, Taylor P, Benito Y, Freydiere AM, et al. Contribution of a broad range polymerase chain reaction to the diagnosis of osteoarticular infections caused by Kingella kingae: description of twenty-four recent pediatric diagnoses. Pediatr Infect Dis J 2005;24(8):692-6.
8. Bradley JS, Kaplan SL, Tan TQ, Barson WJ, Arditi M, Schutze GE, et al. Pediatric pneumococcal bone and joint infections. The Pediatric Multicenter Pneumococcal Surveillance Study Group (PMPSSG). Pediatrics 1998;102(6):1376-82.
9. Kaplan S, Barson, WJ, Ling-Lin, P et al. . Early Trends for Invasive Pneumococcal Infections in Children Following the Introduction of the 13-Valent Pneumococcal Conjugate Vaccine. Pediatr Infec Dis J. 2013
10. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis 2011;52(3):285-92.
11. Martinez-Aguilar G, Hammerman WA, Mason EO, Jr., Kaplan SL. Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* in children. Pediatr.Infect.Dis.J. 2003;22(7):593-598.
12. Chen CJ, Chiu CH, Lin TY, Lee ZL, Yang WE, Huang YC. Experience with linezolid therapy in children with osteoarticular infections. Pediatr Infect Dis J 2007;26(11):985-8.
13. Erturan G, Holme H, Smith R, Dodds R, Iyer S. Successful use of daptomycin in Panton-Valentine leucocidin positive Staphylococcus aureus paediatric osteomyelitis. Int J Surg Case Rep 2012;3(7):238-41.
14. Peltola H, Paakkonen M, Kallio P, Kallio MJT, and the Osteomyelitis-Septic Arthritis Study Group. Short-versus Long-Term Antimicrobial Treatment for Acute Hematogenous Osteomyelitis of Childhood: Prospective, Randomized Trial on 131 Culture-Positve Cases. Pediatr Infec Dis J In Press.
15. Peltola H, Paakkonen M, Kallio P, Kallio MJ. Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. Clin Infect Dis 2009;48(9):1201-10.

16. Ruebner R, Keren R, Coffin S, Chu J, Horn D, Zaoutis TE. Complications of central venous catheters used for the treatment of acute hematogenous osteomyelitis. Pediatrics 2006;117(4):1210-1215.
17. Farrell DJ, Castanheira M, Mendes RE, Sader HS, Jones RN. In vitro activity of ceftaroline against multidrug-resistant Staphylococcus aureus and Streptococcus pneumoniae: a review of published studies and the AWARE Surveillance Program (2008-2010). Clin Infect Dis 2012;55 Suppl 3:S206-14.
18. Corey GR, Wilcox MH, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv41-51.
19. Wilcox MH, Corey GR, Talbot GH, Thye D, Friedland D, Baculik T. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65 Suppl 4:iv53-iv65.
20. Jacqueline C, Amador G, Caillon J, Le Mabecque V, Batard E, Miegeville AF, et al. Efficacy of the new cephalosporin ceftaroline in the treatment of experimental methicillin-resistant Staphylococcus aureus acute osteomyelitis. J Antimicrob Chemother 2010;65(8):1749-52.
21. Lin JC, Aung G, Thomas A, Jahng M, Johns S, Fierer J. The use of ceftaroline fosamil in methicillin-resistant Staphylococcus aureus endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. J Infect Chemother 2012.