CLINICAL REVIEW

Application Type	Pediatric Efficacy Supplements
Application Number(s)	NDA 200327 SD478 S-16 and S-17
Priority or Standard	Priority
Submit Date	7 December 2015
Received Date	7 December 2015
PDUFA Goal Date	7 June 2016
Division/Office	Division of Anti-Infective Products/ OAP/ OND/ CDER
Reviewer Name	Sheral S. Patel, M.D.
Team Leader	Hala Shamsuddin, M.D.
Review Completion Date	13 May 2016
Established Name	Ceftaroline fosamil
(Proposed) Trade Name	Teflaro®
Applicant	Cerexa, Inc. (A Subsidiary of Forest Laboratories, LLC.)
Formulation(s)	Powder for Injection
Dosing Regimen	1. Children aged 2 months to < 2 years: 8 mg/kg every 8 hours IV administered over 5 to 60 minutes 2. Children and adolescents aged 2 years to ≤ 18 years: 12 mg/kg (up to a maximum of 400 mg for pediatric patients weighing > 33 kg) q8h by IV infusion administered over 5 to 60 minutes
Applicant Proposed Indication(s)/Population(s)	For the pediatric population 2 months to < 18 years 1. Acute bacterial skin and skin structure infections 2. Community acquired bacterial pneumonia
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the pediatric population 2 months to < 18 years 1. Acute bacterial skin and skin structure infections 2. Community acquired bacterial pneumonia

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Glossary

%*f*T > MIC	percentage of time during a dosing interval that the free drug concentration exceeds the minimum inhibitory concentration
ABSSSI	acute bacterial skin and skin structure infections
AC	advisory committee
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AWARE	Assessing Worldwide Antimicrobial Resistance Evaluation
BRF	Benefit Risk Framework
CABP	community-acquired bacterial pneumonia
CA-MRSA	community-acquired methicillin-resistant *Staphylococcus aureus*
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CI	confidence interval
Cmax	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
cSSSI	complicated skin and skin structure infections
DAIP	Division of Anti-infective Products
DMC	data monitoring committee
ECG	electrocardiogram
EOIV	end-of-intravenous study drug
EOT	end-of-therapy
ESBL	extended-spectrum beta-lactamases
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonization
IgG	immunoglobulin G
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	Intent-to-Treat
IV	intravenous

LFU	late-follow-up
MDRSP	multidrug-resistant *Streptococcus pneumoniae*
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	Modified Intent-to-Treat
mMITT	microbiological Modified Intent-to-Treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NDA	New Drug Application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PADER	Periodic Adverse Drug Event Report
PBRER	Periodic Benefit-Risk Evaluation Report
PBP	penicillin-binding protein
PCS	potentially clinically significant
PCV	pneumococcal conjugate vaccine
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
PRSP	penicillin-resistant *Streptococcus pneumoniae*
PSUR	Periodic Safety Update report
q6h	every 6 hours
q8h	every 8 hours
q12h	every 12 hours
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
sNDA	supplemental New Drug Application
TEAE	treatment-emergent adverse event
TOC	test-of-cure
VISA	vancomycin-intermediate *Staphylococcus aureus*
VRSA	vancomycin-resistant *Staphylococcus aureus*

1 Executive Summary

1.1. Product Introduction

Ceftaroline fosamil (Teflaro®) is the prodrug of ceftaroline, a cephalosporin antibacterial with in vitro activity against Gram-positive and Gram-negative bacteria. Ceftaroline binds to essential penicillin-binding proteins (PBPs) and is bactericidal.

Ceftaroline fosamil is currently approved for the treatment of two indications in patients ≥ 18 years of age:[1]

1. Acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

2. Community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca*, and *Escherichia coli*.

The currently recommended dosage of Teflaro is 600 mg administered every 12 hours by intravenous (IV) infusion over 5 to 60 minutes in patients ≥ 18 years of age.[1] Dosage adjustments for patients with renal impairment are required. The recommended duration of treatment is 5 to 14 days for ABSSSI and 5 to 7 days for CABP.

In this submission (NDA 200327 SD478 S-16 and S-17), the Sponsor proposes the following:

1. Expand the adult indications of ABSSSI and CABP, to include the pediatric population of children 2 months to < 18 years of age.
2. Dosage of ceftaroline fosamil for pediatric patients, infused over 5 to 60 minutes:
    - Children > 2 years to < 18 years: 12 mg/kg q8h up to a maximum of 400 mg q8h for subjects weighing > 33 kg
    - Children 2 months to < 2 years: 8 mg/kg q8h
3. Treatment duration of 5 to 14 days for both the ABSSSI and CABP indications in patients 2 months to < 18 years.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Sponsor's proposal to expand the adult indications of ABSSSI and CABP for ceftaroline fosamil, and include the pediatric population of children 2 months to < 18 years of age, is acceptable. The Sponsor's studies suggest that children experience known adverse reactions observed in the adult population when exposed to ceftaroline fosamil for approved indications, as well as the cephalosporin antibacterial class in general. Efficacy in the pediatric population is extrapolated based on similarities of the disease process in the adult population. The active-controlled pediatric studies for ABSSSI and CABP conducted by the Sponsor were not powered for comparative inferential analyses. Nevertheless, the pediatric active controlled studies for ABSSSI and CABP provide supportive evidence of the efficacy of ceftaroline fosamil in children 2 months to < 18 years of age

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Both ABSSSI and CABP are considered serious conditions. If ABSSSI or CABP is left untreated, severe infections or life-threatening invasive disease can result. Current intravenous and oral treatment options for ABSSSI and CABP include beta-lactams, such as cephalosporins, as well as drugs from a variety of other antibacterial classes. Ceftaroline fosamil, a cephalosporin, provides antibacterial coverage against select Gram-positive and Gram-negative pathogens frequently causing ABSSSI and CABP.

Efficacy in the pediatric population is extrapolated based on similarities of the disease process in the adult population. The active-controlled pediatric studies for ABSSSI and CABP conducted by the Sponsor were not powered for comparative inferential analyses. Nevertheless, the pediatric active controlled studies for ABSSSI and CABP provide supportive evidence of the efficacy of ceftaroline fosamil in children 2 months to less than 18 years of age.

Highlights of the studies are described by indication.

a. ABSSSI:

The Sponsor conducted a randomized, observer-blinded study comparing ceftaroline fosamil to active comparator (vancomycin or cefazolin) in pediatric patients 2 months to less than 18 years of age. Clinical response in the MITT population at Study Day 3 and at TOC was comparable in the pediatric and adult studies, and no subject had a relapse at LFU in either treatment arm.

b. CABP:

The Sponsor combined results from two studies, Study P903-31 and Study P903-24, to support efficacy for the CABP indication in pediatric patients 2 months to less than 18 years of age. Study P903-31 compared ceftaroline to ceftriaxone in hospitalized patients with CABP, and study (P903-24) compared ceftaroline to ceftriaxone plus vancomycin in hospitalized patients with complicated CABP.

For both studies, clinical response rates in the MITT population at Study Day 4 and at TOC were similar for ceftaroline- and comparator-treated, and comparable to adult studies. No subject had a relapse at LFU in either treatment arm.

Overall, the safety profile of ceftaroline fosamil, when used in the pediatric population studied (426 subjects enrolled and 421 receiving at least 1 dose of study drug), is similar to that described in the adult population, as well as cephalosporin class in general.

The Sponsor proposes an infusion duration in pediatrics of 5 to 60 minutes, which was not used in any of the clinical studies. This infusion duration is acceptable from a safety and clinical pharmacology perspective, even in the youngest age cohort, 2 months to less than 24 months.

In conclusion**,** the pediatric studies provide evidence that the safety profile of ceftaroline fosamil is similar to that observed in the adult population, and support extrapolation of efficacy from the adult population. This reviewer recommends **approval** of ceftaroline fosamil for the treatment of ABSSSI and CABP caused by select susceptible organisms in children 2 months to less than 18 years. Labelling changes will be updated to include pediatric specific data in the following sections: Dosage and Administration, Adverse Reactions for Pediatrics, Pediatric Use and Clinical Studies. In addition, the Postmarketing Adverse Reactions section will be updated to include 'leukopenia'.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• During the emergence and spread of community-acquired methicillin-resistant *Staphylococcus aureus*, pediatric emergency department encounters, hospitalizations, and operative interventions for SSSTI have increased.[2, 3] • Hospital discharges for pediatric community acquired pneumonia (irrespective of pathogen, bacterial or viral) were similar in 1997 (pre-pneumococcal conjugate vaccine) and 2006 (post-pneumococcal conjugate vaccine).[4] • Furthermore, pediatric community acquired pneumonia associated complications, as measured by the rate of hospital discharges, increased between 1997 and 2006, with empyema as the primary complication identified.[4]	• ABSSSI and CABP are serious conditions in the pediatric population. • If ABSSSI or CABP is left untreated, severe infections or life-threatening invasive disease can result.
Current Treatment Options	• There are Infectious Diseases Society of America (IDSA) recommended and/or FDA-approved treatments for ABSSSI and CABP available for both adults and children. • In both adults and pediatrics, IDSA recommends intravenous and oral treatment options for ABSSSI and CABP from a variety of antibacterial classes, including beta-lactams and cephalosporins.[5, 6] • In addition, there are recent FDA-approved treatments for ABSSSI and CABP in adults which are not included in the IDSA Guidelines (i.e. ABSSSI indication: tedizolid phosphate, oritavancin and dalbavancin).	• There are a number of treatment options available to treat ABSSSI and CABP in adult and pediatric populations.
Benefit	• Ceftaroline fosamil, a cephalosporin, provides antibacterial coverage against select Gram-positive and Gram-negative pathogens frequently causing ABSSSI and CABP. • Efficacy of ceftaroline fosamil for the treatment of ABSSSI and CABP in the adult population has been previously established. *Pediatric ABSSSI* • In a randomized, observer-blinded study (P903-23) comparing ceftaroline fosamil to active comparator (vancomycin or cefazolin) in pediatric subjects 2 months to less than 18 years of age, clinical response in the MITT population at Study Day 3 and at TOC was similar in the pediatric and adult studies. • There was no relapse at LFU in either treatment arm of the pediatric studies. *Pediatric CABP* • Two randomized, observer-blinded pediatric studies for CABP were conducted in pediatric subjects 2 months to less than 18 years. The first study compared ceftaroline to ceftriaxone in hospitalized patients with CABP (P903-31). The second study (P903-24) compared ceftaroline to ceftriaxone plus	• In addition to extrapolation from the adult studies, the efficacy of ceftaroline fosmail for the treatment of ABSSSI and CABP in pediatrics (2 months to less than 18 years) is supported by three randomized observer-blinded clinical trials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	vancomycin in hospitalized patients with complicated CABP. • For both studies, clinical response rates in the MITT population at Study Day 4 and at TOC were similar for ceftaroline- and comparator-treated arms, and comparable to adult studies. • No subject had a relapse at LFU in either treatment arm of the pediatric studies.	
Risk	• The pediatric safety database for ceftaroline fosamil includes patients from 5 clinical studies and is adequate (426 subjects enrolled and 421 receiving at least 1 dose of study drug) [Group 1: ABSSSI (P903-23), CABP (P903-31 and P903-24); Group 2: PK studies (P903-15 and P903-21)]. • Most TEAEs occurred at a similar incidence in both treatment arms of the Group 1 studies. • Similar to adults, rash and Direct Coombs' test seroconversion occurred at a higher incidence in the ceftaroline group than the comparator group in the pediatric population. • Adverse reactions occurring at ≥ 3% in the ceftaroline fosamil arm of the pooled Group 1 pediatric studies include 'diarrhea', 'nausea', 'vomiting', 'pyrexia' and 'rash'. • Additional TEAEs occurring at ≥ 2% in the ceftaroline fosamil arm of the pooled Group 1 pediatric studies include 'abdominal pain', 'gastroenteritis', 'aspartate aminotransferase increased', 'alanine aminotransferase increased', 'headache', 'cough', 'dermatitis diaper' and 'pruritus'. • The Sponsor proposes a 5 to 60 minute infusion duration based on simulations. After the 5 minute infusion duration, the C_{max} in children 2 months to < 6 months was similar to adults, adolescents and children 6 months to 2 years. The C_{max} in children 2 months to < 6 months is lower than the C_{max} in children 2 years to < 12 years. Finally, the exposure in the 2 months to < 6 months cohort is similar to the mean C_{max} observed in adult single dose PK studies. • Safety data support a 5 to 60 minute infusion duration in the pediatric population. Pre-clinical studies suggest that there is a 20 to 28 fold safety margin for ceftaroline. An adult PK and tolerability study comparing ceftaroline fosamil infusion durations of 5 and 60 minutes did not identify safety concerns. Ceftaroline belongs to the widely used cephalosporin class, where safety issues are well described. • In two consecutive PADERS, neutropenia/leukopenia was noted to occur at a rate of 22% amongst spontaneously reported cases.	• The safety profile of ceftaroline fosamil in the pediatric population studied is similar to that described in the adult population, as well as cephalosporin class in general. • A 5 to 60 minute infusion duration in the pediatric population (2 months to less than 18 years) is acceptable from a safety and clinical pharmacology perspective. • Labeling should include the adverse event 'leukopenia' in the Post-marketing Adverse Events Section.
Risk Management	• The cephalosporin antibacterial class antibacterials has a well-documented safety profile in adults and children. • The safety concerns associated with ceftaroline fosmail use in adults for ABSSSI and CABP is reflected in current labeling. • The Sponsor has addressed PREA related PMRs for ABSSSI and CABP studies in pediatric subjects.	• No new safety concerns are identified with ceftaroline fosamil treatment for ABSSSI and CABP in the pediatric population.

2 Therapeutic Context

2.1. Analysis of Condition

2.1.1 Acute Bacterial Skin and Skin Structure Infections

The FDA Guidance for Industry on Acute Bacterial Skin and Skin Structure Infections defines ABSSSI in clinical trials as a bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration).[7] The minimum area of involvement of 75 cm^2 was chosen to select patients with acute bacterial skin infections for which a reliable control drug treatment effect can be estimated using noninferiority trial designs.[7]

The Guidance describes three main infection types to consider when enrolling patients in ABSSSI clinical trials: [7]

1. Cellulitis/erysipelas: A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration

2. Wound infection: An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration

3. Major cutaneous abscess: An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration

Empiric antibiotic therapy for ABSSSI should account for the most-likely pathogens causing infection, including resistant organisms. Bacterial pathogens frequently causing ABSSSI include *Streptococcus pyogenes* and *Staphylococcus aureus,* including methicillin-resistant *S. aureus* (MRSA). Less frequent causes of ABSSSI include other Streptococcus species, *Enterococcus faecalis*, or Gram-negative bacteria.[7]

A variety of treatment approaches for ABSSSI can be utilized, including antibiotics and incision and drainage. During the emergence and spread of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), pediatric emergency department encounters, hospitalizations, and operative interventions for SSSTI have increased.[2, 3] However, local complications or life-threatening invasive disease can result if left untreated.

2.1.2 Community Acquired Bacterial Pneumonia

The FDA Guidance for Industry on Community-Acquired Bacterial Pneumonia provides a specific definition of CABP used in clinical trials.[8] According to the Guidance, CABP is defined as an acute bacterial infection of the pulmonary parenchyma associated with chest pain, cough, sputum production, difficulty breathing, chills, rigors, fever, or hypotension, and is accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph.[8]

Pulmonary, metastatic, or systemic life-threatening complications can result if CABP is left untreated.[6] These complications include, and are not limited to, pleural effusion, empyema, pneumothorax, lung abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory failure, meningitis, central nervous system abscess, pericarditis, endocarditis, osteomyelitis, septic arthritis, systemic inflammatory response syndrome or sepsis and hemolytic uremic syndrome.[6]

Empiric antibiotic therapy for CABP should account for the most-likely pathogens causing infection, including resistant organisms. Typical bacterial pathogens causing CABP include *Streptococcus pneumoniae*, *Haemophilus influenzae, Staphylococcus aureus*, and *Moraxella catarrhalis*. Atypical bacterial pathogens causing CABP include *Chlamydophila pneumoniae, Mycoplasma pneumoniae*, and *Legionella pneumophila*.

Pneumococcal and *Haemophilus influenza* type b (Hib) conjugate vaccines have reduced the incidence of pneumonia caused by these pathogens over the past 30 years.[9, 10] However, the overall rates of hospital discharges for pediatric community acquired pneumonia (irrespective of pathogen, bacterial or viral) were similar in 1997 (pre-pneumococcal conjugate vaccine) and 2006 (post-pneumococcal conjugate vaccine).[4] In addition, the rate of discharges with any pediatric community acquired pneumonia associated complication increased between 1997 and 2006 by 28% (11.8 and 15.1 per 100,000 population, respectively).[4] Ninety-seven percent of the complications documented in the aforementioned study were empyema.[4]

2.2. Analysis of Current Treatment Options

2.2.1 Acute Bacterial Skin and Skin Structure Infections

Depending on the age of the child, type and severity of the lesion, as well as the presence or absence of purulence, 2014 Infectious Diseases Society of America (IDSA) Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections recommends intravenous antibiotics, oral antibiotics, incision and drainage and/or surgical debridement.[5]

Intravenous antibiotics recommended by the IDSA for the treatment of ABSSSI include vancomycin, daptomycin, linezolid, televancin, piperacillin/ tazobactam, penicillin, ceftriaxone,

cefazolin, nafcillin, clindamycin, doxycycline, ceftazidime, and ciprofloxacin.[5] In addition, tedizolid phosphate, oritavancin and dalbavancin for FDA-approved therapies for ABSSSI in adults.

Oral antibiotics recommended for the treatment of ABSSSI include penicillin VK, oral cephalosporins, dicloxacillin, clindamycin and trimethoprim-sulfamethoxazole.[5]

2.2.2 Community Acquired Bacterial Pneumonia

Depending on the severity of the pneumonia, likely infecting pathogens and age of the child, the 2011 Infectious Diseases Society of America Practice Guidelines for the Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age recommend intravenous antibiotic treatment, oral antibiotic treatment, as well as adjunctive surgical and non-antibiotic therapy.[6]

Intravenous antibiotics recommended for the treatment of CABP in pediatrics include ampicillin, penicillin, ceftriaxone, cefotaxime, clindamycin, vancomycin, cefazolin, oxacillin, nafcillin, linezolid, ciprofloxacin, azithromycin, and erythromycin.[6]

Oral antibiotics recommended for the treatment of CABP in pediatrics include amoxicillin, amoxicillin-clavulanate, second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil, cefdinir, cefixime, ceftibuten), levofloxacin, linezolid, clindamycin, cephalexin, azithromycin, clarithromycin, doxycycline, levofloxacin, and moxifloxacin.[6]

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The original NDA for ceftaroline fosamil (Teflaro®) was approved on 29 October 2010. At the time of NDA approval, the Sponsor was assigned five post-marketing requirements under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

The required studies are listed from the original NDA approval.

1692-001: Single dose pharmacokinetic trial

Perform a trial in pediatric patients being treated concomitantly with antibacterial agent(s) to evaluate single dose pharmacokinetic parameters and assess safety of Teflaro® (ceftaroline fosamil) in all pediatric age groups.

Five age cohorts must be studied as follows:

- Group 1: children from 6 to less than 12 years
- Group 2: children from 24 months to less than 6 years
- Group 3: infants/toddlers from 28 days to less than 24 months
- Group 4: term neonates less than 28 days; (stratification within the group: 0-14 days; >14 days to <28 days)
- Group 5: pre-term neonates less than 28 days (stratification within the group: 0-14 days; >14 days to <28 days)

There must be a minimum of 8 evaluable subjects per cohort. In Group 3, there will be an equal representation of patients aged 28 days to <12 months and ≥12 months to <24 months.

1692-002: Perform a randomized comparison of Teflaro® (ceftaroline fosamil) and comparator in pediatric subjects with CABP utilizing an enrichment strategy for enrollment of patients with methicillin-resistant *Staphylococcus aureus* (MRSA). Pediatric patients under 17 years of age with CABP must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).

1692-003: Perform a randomized comparison of Teflaro® (ceftaroline fosamil) and comparator in pediatric subjects with ABSSSI including patients with infection suspected or demonstrated to be caused by MRSA. Pediatric patients under 17 years of age with ABSSSI must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).

1692-004: Cerebrospinal Fluid (CSF) Concentration Trial Perform a trial assessing the CSF concentration profile of Teflaro® (ceftaroline fosamil) in infants < 2 months of age. A minimum of 12 infants < 2 months of age receiving antibacterials for treatment of late-onset neonatal sepsis must be studied.

1692-005: Perform a randomized comparison of Teflaro® (ceftaroline fosamil) and comparator in infants < 2 months of age with ABSSSI and CABP including patients with infections suspected or demonstrated to be caused by MRSA.

This current submission (S-16 and S-17) addresses (b) (4) 1692-002, and 1692-003.

3.2. Summary of Presubmission/Submission Regulatory Activity

A summary of key FDA regulatory interactions regarding the pediatric drug development program for PMR 1692-001, 1692-002, and 1692-003 are summarized in **Table 1**.

Table 1 Summary of Key Regulatory Interactions

Date	Description	Key Points
30 December 2009	Original NDA	P903-15 (Adolescent PK Study) submitted (SN 0000).
29 October 2010	NDA Approval	Approved for use in adults with ABSSSI and CABP.
18 April 2011	Type C Meeting	Agreement to conduct pre-clinical animal studies and epithelial lining fluid study. Agreement to enroll 120 ceftaroline-treated subjects in the CABP studies and 180 ceftaroline-treated subjects in ABSSSI study, for goal of 300 ceftaroline-treated pediatric subjects.
10 August 2011	Type C Meeting	Agreement to conduct two studies to satisfy pediatric CABP studies (P903-31 and P903-24) (SN 0065).
20 June 2012	Type B Meeting	Concurrence on proposed dose for the pediatric and adult CABP studies enriched for MRSA.
30 September 2013	Type C Meeting	Modification and/ or release of PMRs. Agreement to allow reduced enrollment in P903-31 (CABP) and P903-24 (complicated CABP). Released from PMR 1692-007, adult complicated CABP study (P903-25).
04 December 2013	PMR 1692-001	P903-21 (Single dose pediatric PK) CSR submitted (SN 0110).
30 October 2014	PMR 1692-002	P903-31 (CABP) CSR submitted (SN 0114).
19 November 2014	PMR 1692-002	P903-24 (complicated CABP) CSR submitted (SN 0116).
25 November 2014	PMR 1692-003	P903-23 (ABSSSI) (SN 0117).
21 May 2015	Type B Pediatric pre-sNDA Meeting	1. Efficacy data for the pediatric studies in subjects in ABSSSI would be presented separately rather than integrated with data from pediatric studies in CABP. 2. Efficacy data for the 2 CABP studies (Study P903-31 and Study P903-24) did not need to be integrated because the studies represent different populations and different doses of ceftaroline. 3. Safety data from all 3 active-controlled pediatric studies were pooled. 4. Safety cut-off date for the 120 day safety update report would be the pediatric sNDA submission date. 5. Division requested that relevant safety and efficacy results from the clinical trials in adult subjects with complicated skin and skin structure infections (cSSSI) (pooled Studies P903-06 and P903-07) and clinical trials in

		adult subjects with CABP (pooled Studies P903-08 and P903-09) be referenced in the pediatric supplemental New Drug Application (sNDA) to facilitate comparisons between adult and pediatric populations.
07 December 2015	Pediatric sNDA	NDA submitted to expand indications of ABSSSI and CABP to pediatric population.

3.3. Foreign Regulatory Actions and Marketing History

Ceftaroline fosamil was approved as Zinforo® by the European Medicines Agency (EMA) on 23 August 2012 for the treatment of community acquired pneumonia and complicated skin and skin structure infections. A Pediatric Investigation Plan (EMEA-000769-PIP01-09-M05) was agreed upon and a deferral was granted for ceftaroline fosamil on 6 September 2010. (b) (4)

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

On 22 February 2016, a consult was sent to the Office of Study Integrity and Surveillance (OSIS) to inspect analytic sites for the pediatric studies. Per the Clinical Pharmacology reviewer, Kunyi Wu, PharmD, "*Since the pediatric dose selection in this submission was based on the approach of full extrapolation, the pharmacokinetics data in pediatric patients are critical for the pediatric dose recommendations".* The sites are (b) (4)

A report of the OSIS inspections are pending at the time of this review.

4.2. Product Quality

The ceftaroline fosamil drug product used in the pediatric clinical studies is the same formulation as the currently marketed product. The Sponsor did not conduct additional formulation development or biopharmaceutical studies for this submission.

Please refer to the original Chemistry Manufacturing and Controls NDA review by Dr. Andrew Yu, for additional details. Please refer to the CMC review by Dr. Shrikant Pagay for details regarding this supplement.

4.3. Clinical Microbiology

Ceftaroline has activity against Gram-positive and Gram-negative micro-organisms, including methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumonia*.

In order to meet postmarketing commitments, the Sponsor conducted annual surveillance in the United States on key pathogens listed on the ceftaroline fosamil package insert to monitor any changes in ceftaroline susceptibility over time. The US AWARE (Assessing Worldwide Antimicrobial Resistance Evaluation) surveillance program includes bacterial isolates collected from skin and respiratory specimen sources from children aged less than 18 years.

Skin and respiratory pathogens collected from US children in the 2013 AWARE surveillance program exhibit similar susceptibility profiles to isolates previously identified from adult subjects.

Please refer to the original NDA Clinical Microbiology review, as well as the review for this supplement, by Avery Goodwin, PhD, for additional details.

4.4. Nonclinical Pharmacology/Toxicology

The Sponsor submits results of several toxicology studies to support the original NDA including single- and repeat- dose (up to 3 months for ceftaroline fosamil), reproductive and developmental toxicity, and genotoxicity studies. Please refer to the original Pharmacology-Toxicology NDA review by Amy Ellis, PhD, for details.

In this submission, the Sponsor submits reports on additional toxicity studies conducted in juvenile rats. This includes a 14 day dose range finding juvenile toxicity study in neonatal rats and a 14 day juvenile toxicity study in neonatal rats.

In the juvenile toxicity studies, ceftaroline fosamil was dosed to male and female neonatal rats by slow intravenous bolus dose for 14 days from postnatal day 7 to 21. The NOAEL was the highest dose tested (270 mg/kg). In humans, the intended doses of ceftaroline fosamil in pediatric patients with normal renal function and mild renal impairment are 12 mg/kg (up to a maximum dose of 400 mg) administered every 8 hours as a 1 hour infusion to pediatric patients ≥ 2 years and 8 mg/kg ceftaroline fosamil every 8 hours as a 1 hour infusion in children 2 months to < 2 years.

Ceftaroline exposure levels ($AUC_{(0-t)}$) tested in the juvenile rat at 270 mg/kg/day were approximately 2 to 3-fold higher than the predicted median steady state $AUC_{(0-24)}$ values of ceftaroline (based on simulations) in patients with mild renal impairment. In addition, the

maximum plasma levels of ceftaroline tested in the juvenile rat at 270 mg/kg/day were approximately 20 to 28-fold higher than the predicted median steady state C_{max} values of ceftaroline (based on simulations) in patients with mild renal impairment.

Results from the preclinical studies support the use of ceftaroline fosmail in children, even with an increased C_{max} associated with 5 to 60 minute infusion times. Please refer to the discipline specific review by Amy Ellis, PhD for additional details.

4.5. Clinical Pharmacology

The pediatric Clinical Pharmacology program for ceftaroline fosamil includes data from the following studies:

1. Single dose PK study in pediatric subjects aged 12 to 17 years who were hospitalized and receiving antibiotic therapy other than ceftaroline (Study P903-15, included in the original NDA submission, n=9).

2. Single-dose PK study in pediatric subjects aged birth to < 12 years with a suspected or confirmed infection of any type (Study P903-21, n=53).

3. Sparse PK samples collected in the multiple-dose safety/efficacy studies in pediatric subjects with ABSSSI and CABP (Studies P903-23, P903-24, and P903-31).

Data from Study P903-15 and P903-21 were included in the safety analyses (**Section 8**). Please refer to the Clinical Pharmacology review by Kunyi Wu, PharmD for details regarding Clinical Pharmacology.

4.5.1. Mechanism of Action

Ceftaroline fosamil is a bactericidal beta-lactam antibacterial which targets penicillin-binding proteins (PBP) to inhibit the biosynthesis of the bacterial cell wall.

4.5.2. Pharmacodynamics

The same pharmacodynamic principles used for treating adults with ceftaroline can be applied to children. The pharmacokinetic/pharmacodynamic (PK/PD) index associated with the efficacy of ceftaroline is the percentage of time during a dosing interval that the free drug concentration exceeds the minimum inhibitory concentration (%*f*T > MIC).

4.5.3. Pharmacokinetics

Human Pharmacokinetics

Following IV infusion, ceftaroline fosamil is rapidly converted in plasma to active ceftaroline. In adults, exposure increases in proportion to dose (within the dose range of 50 to 1000 mg) with no accumulation of ceftaroline fosamil or active ceftaroline upon multiple dosing. Maximum plasma concentrations are achieved at the end of infusion in adults, with the elimination half-life ranging 2.0 to 2.6 hours. The primary route of excretion in adults is renal with around 40% to 70% of the dose being excreted in urine as ceftaroline.

In adolescents, the elimination half-life for ceftaroline is 1.9 hours, and the percentage excreted in urine as ceftaroline is 55%.

Population Pharmacokinetic Analyses

As interim PK data from Study P903-21 became available, they were added to the updated population PK model which was then used to conduct simulations to select doses for studies P903-23, P903-24, and P903-31.

The doses selected for Studies P903-23 (ABSSSI) and P903-31 (CABP) were intended to match exposures in adults with normal renal function or mild renal impairment dosed with ceftaroline fosamil 600 mg every 12 hours (q12h).

The doses selected for Study P903-24 (complicated CABP) were intended to match exposures in adults with normal renal function or mild renal impairment dosed with ceftaroline fosamil 600 mg q8h. A dose of 600 mg q8h ceftaroline fosamil is not currently approved in adults, and a pediatric dose regimen that matches such adult exposures is not being sought by the Sponsor at this time.

Infusion duration

The Sponsor previously submitted a supplemental NDA (200327 SD405, S-14) changing the ceftaroline IV infusion rate from 1 hour to a duration of 5 to 60 minutes in adults. A Phase 1 study (CPT-PK-05) in healthy adult subjects was conducted to assess the safety, tolerability and PK of the shorter infusion times. The incidence of TEAEs associated with local tolerability was low and similar in the 5 minute and 60 minute infusion durations. Updated PK/PD target attainment simulations showed that target attainment is similar for the 5 minute and 60 minute infusions for PK/PD targets associated with 1-log kill of *S. aureus* and *S. pneumoniae* at the approved breakpoints for these pathogens. Although the 5-minute infusion results in higher values of C_{max} (1.3-fold higher based on simulations, 1.9-fold higher observed in Study CPT-PK-05), AUC values are similar for both infusion times. The supplement was approved on 31 August 2015 to allow for ceftaroline fosamil infusion over 5 to 60 minutes in adults. For

additional details, please refer to the relevant discipline specific reviews for S-14.

The Sponsor proposes that ceftaroline fosamil can also be administered over 5 to 60 minutes in pediatric patients and provides several reasons. First, the Sponsor reports that pediatric subjects demonstrated similar pharmacokinetics for ceftaroline compared with adult subjects after accounting for weight and maturational changes in renal function. Second, consistent with adult data, the clearance of ceftaroline was similar in pediatric subjects with ABSSSI and CABP, when stratified by age. Finally, the Sponsor believes that the proposed pediatric dose regimens, administered as a 1-hour infusion, demonstrate target attainment that is better than adults across age groups from 2 months to < 18 years.

Reviewer comment: *The Sponsor proposes a 5 minute infusion duration which has not been studied in children.*

From a safety perspective, an infusion duration of 5 to 60 minutes is acceptable in the pediatric population. Pre-clinical studies suggest that there is a 20 to 28 fold safety margin for ceftaroline. The adult PK and tolerability study comparing ceftaroline fosamil infusion durations of 5 and 60 minutes did not identify safety concerns. Ceftaroline belongs to the widely used cephalosporin class, where class-specific safety issues are well described.

Simulations support the use of ceftaroline fosamil with an infusion duration of 5 to 60 minutes. After the 5 minute infusion duration, the C_{max} in children 2 months to less than 6 months was similar to adults, adolescents and pediatric patients 6 months to 2 years. In addition, the C_{max} in children 2 months to less than 6 months is lower than the C_{max} in pediatric patients 2 years to less than 12 years. Finally, the exposure resulting from the proposed dose in children 2 months to less than 6 months is similar to the mean C_{max} observed in single dose PK studies in adults. Please refer to the Clinical Pharmacology Review for additional details.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

A tabular listing of completed studies relevant to this submission is summarized in **Table 2** and **Table 3**. The Sponsor completed 5 studies as part of the pediatric development program: one ABSSSI (P903-23), two CABP (P903-31 and P903-24), and two PK studies (P903-15 and P903-21). Studies P903-23, P903-31, and P903-24 are categorized as Group 1 studies. Studies P903-15 and P903-21 are categorized as Group 2 studies.

Where applicable, results were compared to findings in adult subjects from the adult Phase 3 trials for ABSSSI (studies P903-06 and P903-07) and CABP (P903-08 and P903-09) (**Table 4**).

Table 2 Overview of Group 1 ceftaroline fosamil studies in the pediatric development program.

Study Number	Indication	Study Objectives	Design	Ceftaroline fosamil dosage regimen by treatment	Comparator (s) dosage regimen by treatment	Treatment Duration	Treatment (Sample Size)[a]	Countries
P903-23	Acute bacterial skin and skin structure infections	Safety and tolerability, efficacy, and pharmacokinetics in pediatric subjects ages 2 months to < 18 years	Phase 2/3, observer blinded, active controlled, parallel-group	IV ceftaroline fosamil infused over 60 (± 10) minutes q8h (± 1 hour) as follows: •Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg •Children < 6 months: ceftaroline fosamil 8 mg/kg	IV vancomycin 15 mg/kg q6h (± 1 hour) infused over at least 60 minutes or IV cefazolin 75 mg/kg/day divided q8h (± 1 hour) infused over 60 (± 10) minutes and optional IV aztreonam 30 mg/kg q8h (± 1 hour) infused over 60 (± 10) minutes, if an infection involving a Gram negative pathogen was identified or suspected	5 to 14 days of IV and oral or IV alone; a minimum of 3 days (7 infusions) for ceftaroline group	Ceftaroline[b,c] (n = 106) Vancomycin[c,d,e] or Ceftazolinc,[e,f] (n = 53) 2:1 Randomization	Argentina, Chile, South Africa, Georgia, Latvia, Lithuania, Spain, Poland, and United States
P903-31	Community acquired bacterial pneumonia requiring hospitalization	Safety and tolerability, efficacy, and pharmaco-kinetics in pediatric subjects ages 2 months to	Phase 2/3, observer blinded, active controlled, parallel group	IV ceftaroline fosamil infused over 60 (± 10) minutes q8h (± 1 hour) as follows: •Children ≥ 6 months: ceftaroline fosamil	IV ceftriaxone at a total daily dose of 75 mg/kg/day up to a maximum of 4 g/day infused over 30 minutes (± 10) q12h (± 2)	5 to 14 days of IV and oral or IV alone; a minimum of 3 days (7 infusions) for ceftaroline group	Ceftaroline[b,c] (n = 121) Ceftriaxone[c,h] (n = 39) 3:1 Randomization	Bulgaria, Georgia, Greece, Hungary, Poland, Spain, Ukraine and United

Study Number	Indication	Study Objectives	Design	Ceftaroline fosamil dosage regimen by treatment	Comparator (s) dosage regimen by treatment	Treatment Duration	Treatment (Sample Size)[a]	Countries
		< 18 years		12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg •Children < 6 months: ceftaroline fosamil 8 mg/kg				States
P903-24	Complicated community acquired bacterial pneumonia	Safety and tolerability, efficacy, and pharmacokinetics in pediatric subjects ages 2 months to < 18 years	Phase 4, observer blinded, active controlled, parallel group	Intravenous ceftaroline fosamil infused over 120 (± 10) min q8h (± 1 hour) as follows: •Children ≥ 6 months: ceftaroline fosamil 15 mg/kg for subjects weighing ≤ 40 kg or 600 mg for subjects weighing > 40 kg •Children < 6 months: ceftaroline fosamil 10 mg/kg	IV ceftriaxone at a total daily dose of 75 mg/kg/day up to 4 g/day, given in equally divided doses, each infused over 30 (± 10) min q12h (± 2 hours) IV vancomycin 15 mg/kg q6h (± 1 hour), infused over at least 60 minutes.	5 to 21 days of IV and oral or IV alone; a minimum of 3 days (72 hours)	Ceftaroline[c,g] (n = 30) Ceftriaxone[c,h] and Vancomycin[c,d] (n = 10) 3:1 Randomization	Georgia, Ukraine, and United States

[a] Number of subjects in the Safety Population.

[b] IV ceftaroline fosamil infused over 60 minutes every 8 hours (q8h). Children ≥ 6 months: 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg. Children < 6 months: 8 mg/kg.
[c] Followed by optional oral switch.
[d] IV vancomycin 15 mg/kg infused at least over 60 minutes every 6 hours (q6h).
[e] Plus optional IV aztreonam 30 mg/kg q8h infused over 60 minutes for identified or suspected gram-negative pathogens.
[f] IV cefazolin 75 mg/kg/day divided q8h infused over 60 minutes.
[g] IV ceftaroline fosamil infused over 120 minutes q8h. Children ≥ 6 months: 15 mg/kg for subjects weighing ≤ 40 kg or 600 mg for subjects weighing > 40 kg. Children < 6 months: 10 mg/kg.
[h] IV ceftriaxone 75 mg/kg/day up to 4 g/day divided every 12 hours (q12h) infused over 30 minutes.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety Table 4.1.1.1-1 and Module 5.2 Tabular Listing of All Clinical Studies Table 5.2.

Table 3 Overview of Group 2 ceftaroline fosamil studies in the pediatric development program.

Study Number	Study Objectives	Design	Ceftaroline fosamil dosage	Duration of Infusion	Treatment (Sample Size)[a]	Countries
P903-15	Pharmacokinetics and safety in pediatric subjects ages 12 to 17 years	Phase 1, open-label, noncomparative, single-dose	Single 1-hour IV infusion of ceftaroline fosamil 8 mg/kg for subjects who weighed < 75 kg or 600 mg for subjects who weighed ≥ 75 kg	All doses were single dose 60-min infusions	Ceftaroline (n = 9)	United States
P903-21	Pharmacokinetics, safety, and tolerability in pediatric subjects age < 12 years	Phase 4, open-label, single-dose	IV Dose Cohorts: • Cohort 1: ≥ 6 to < 12 years; 10 mg/kg (max dose of 600 mg for body weight ≥ 60 kg) as a 1-h infusion • Cohort 2: ≥ 2 to < 6 years; 15 mg/kg as a 1.5-h infusion • Cohort 3: ≥ 28 days to < 2 years; 12 mg/kg as a 1-h infusion for age ≥ 5 months and 8 mg/kg as a 1-h infusion for age 28 days to 5 months • Cohort 4: full-term neonates < 28 days; 8 mg/kg as a 1-h infusion • Cohort 5: pre-term neonates (gestational age 35 to 3 7 weeks) < 28 days; 8 mg/kg as a 1-h infusion	Doses were single dose 60-min infusions or 90 minute infusions	Ceftaroline (n = 53) Cohort 1: 10; Cohort 2: 8; Cohort 3: 12; Cohort 4: 12; Cohort 5: 11	United States

[a] Number of subjects who were enrolled and received treatment.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety Table 4.1.1.2-1 and Module 5.2 Tabular Listing of All Clinical Studies Table 5.2.

Table 4 Overview of Phase 3 adult ceftaroline fosamil studies reviewed in the original NDA.

Study Number	Indication	Study Objectives	Design	Ceftaroline fosamil dosage regimen by treatment	Comparator (s) dosage regimen by treatment	Treatment Duration	Treatment (Sample Size)[a]	Countries
P903-06	Complicated bacterial skin and skin structure infections	To determine non-inferiority in clinical cure rate of ceftaroline compared with vancomycin plus aztreonam at TOC	Multicenter, randomized, double-blind, comparative study	Ceftaroline fosamil 600 mg q12h, IV over 1 hour followed by placebo, q12h, IV over 1 hour (Note: ceftaroline fosamil dose could be adjusted based on renal impairment)	Vancomycin 1 g q12h, IV over 1 hour, followed by aztreonam 1 g q12h, IV over 1 hour (Note: vancomycin dose could be adjusted based on local guidelines or weight)	5 to 14 days; extension up to 21 days could be approved by Sponsor	Ceftaroline (n = 351) Vancomycin plus Aztreonam (n = 347) 1:1 Randomization	Multiple
P903-07	Complicated bacterial skin and skin structure infections	To determine non-inferiority in clinical cure rate of ceftaroline compared with vancomycin plus aztreonam at TOC	Multicenter, randomized, double-blind, comparative study	Ceftaroline fosamil 600 mg q12h, IV over 1 hour followed by placebo, q12h, IV over 1 hour (Note: ceftaroline fosamil dose could be adjusted based on renal impairment)	Vancomycin 1 g q12h, IV over 1 hour, followed by aztreonam 1 g q12h, IV over 1 hour (Note: vancomycin dose could be adjusted based on local guidelines or weight)	5 to 14 days; extension up to 21 days could be approved by Sponsor	Ceftaroline (n = 341) Vancomycin plus Aztreonam (n = 339) 1:1 Randomization	Multiple

Study Number	Indication	Study Objectives	Design	Ceftaroline fosamil dosage regimen by treatment	Comparator (s) dosage regimen by treatment	Treatment Duration	Treatment (Sample Size)[a]	Countries
P903-08	Community acquired bacterial pneumonia	To determine non-inferiority in clinical cure rate for ceftaroline compared to ceftriaxone at TOC	Multicenter, randomized, double-blind, comparative study	Ceftaroline fosamil 600 mg q12h, IV. (administered as 2 consecutive 30-minute IV infusions of 300 mg each) (Note: ceftaroline fosamil dose could be adjusted based on renal impairment) Adjunctive therapy: 2 doses oral clarithromycin starting on Study Day 1	Ceftriaxone 1 g q24h, IV over 30 minutes followed by saline placebo, q24h, IV over 30 minutes Adjunctive therapy: 2 doses oral clarithromycin starting on Study Day 1	5 to 7 days	Ceftaroline (n = 298) Ceftriaxone (n = 308) 1:1 Randomization	Multiple
P903-09	Community acquired bacterial pneumonia	To determine non-inferiority in clinical cure rate for ceftaroline compared to ceftriaxone	Multicenter, randomized, double-blind, comparative study	Ceftaroline fosamil 600 mg q12h, IV. (administered as 2 consecutive 30-minute IV infusions of 300 mg each)	Ceftriaxone 1 g q24h, IV over 30 minutes followed by saline placebo, q24h, IV over 30 minutes	5 to 7 days	Ceftaroline (n = 310) Ceftriaxone (n = 303) 1:1 Randomization	Multiple

Study Number	Indication	Study Objectives	Design	Ceftaroline fosamil dosage regimen by treatment	Comparator (s) dosage regimen by treatment	Treatment Duration	Treatment (Sample Size)[a]	Countries
		at TOC		(Note: ceftaroline fosamil dose could be adjusted based on renal impairment)				

5.2. Review Strategy

The Sponsor completed 5 clinical studies in their pediatric development program for ceftaroline fosamil (ABSSSI [P903-23], CABP [P903-31 and P903-24], and PK [P903-15 and P903-21]). Supportive efficacy data were evaluated in the active-controlled studies P903-23, P903-31, and P903-24. The safety review included an analysis of data from all 5 clinical studies. Results from the original NDA review are presented to compare findings in the pediatric population with adults. Please refer to the original NDA discipline-specific reviews of ceftaroline fosamil for additional details.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study P903-23: A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Ceftaroline Versus Comparator in Pediatric Subjects With Acute Bacterial Skin and Skin Structure Infections (D3720C00004)

6.1.1. Study Design

Overview and Objective

Study P903-23 aimed to evaluate the safety, efficacy, and PK of intravenous (IV) ceftaroline versus IV comparator (vancomycin or cefazolin with or without aztreonam) in pediatric subjects from the ages of 2 months to < 18 years with ABSSSI. The trial primarily assessed safety and was not powered for formal efficacy evaluations.

- **Primary Objective**
  To evaluate the safety and tolerability of ceftaroline versus comparator in pediatric subjects, ages 2 months to < 18 years, with acute bacterial skin and skin structure infections (ABSSSI)

- **Secondary Objective**
  1. Evaluate the efficacy of ceftaroline versus comparator in pediatric subjects ages 2 months to < 18 years with ABSSSI
  2. Evaluate the pharmacokinetics (PK) of ceftaroline in pediatric subjects ages 2 months to < 18 years with ABSSSI

Trial Design

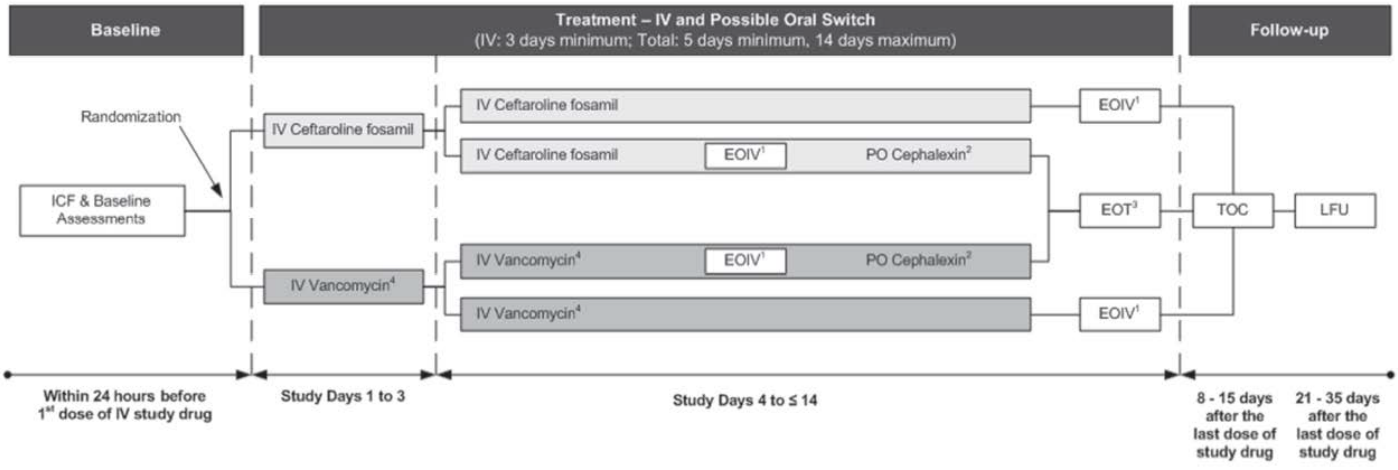
Basic Study Design

Study P903-23 was a phase 2/3 multicenter, randomized, observer-blinded, active-controlled, parallel-group study evaluating IV ceftaroline versus IV comparator (vancomycin or cefazolin with or without aztreonam) in pediatric subjects from the ages of 2 months to < 18 years with ABSSSI (**Figure 1**). If an infection involving a Gram-negative pathogen was identified or suspected, aztreonam was available for administration during IV treatment with comparator. Subjects were stratified by age, cohort and region and were randomly assigned to treatment in a 2:1 ratio, ceftaroline to comparator.

There were four cohorts of descending age:

- Cohort 1: children from 12 years to < 18 years
- Cohort 2: children from 6 years to < 12 years
- Cohort 3: children from 24 months to < 6 years
- Cohort 4: young infants/toddlers from 2 months to < 24 months

Figure 1 Study P903-23: Study Design



Abbreviations: EOIV = End-of-Intravenous Study Drug Therapy; EOT = End-of-Therapy; ICF = informed consent form; IV = intravenous; LFU = Late Follow-up; PO = by mouth; TOC = Test-of-Cure.
[1] EOIV = within 24 hours after the last dose of IV study drug and before switch to PO study drug (if applicable).
[2] PO cephalexin, clindamycin, or linezolid; PO switch allowed on or after Study Day 4 per protocol.
[3] EOT = within 48 hours after the last dose of PO study drug.
[4] IV vancomycin or cefazolin; plus optional aztreonam.

Source: NDA 200327 Clinical Study Report for P903-23, Figure 9.1-1, Study Design.

On, or after Study Day 4, subjects meeting pre-defined criteria could switch from IV to open label oral study drug.

Study treatments were as follows:

- Ceftaroline fosamil
  IV ceftaroline fosamil infused over 60 (± 10) minutes every 8 hours (q8h) (± 1 hour) as follows:
  - Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg
  - Children < 6 months: ceftaroline fosamil 8 mg/kg
- Comparator
  - IV vancomycin 15 mg/kg every 6 hours (q6h) (± 1 hour) infused over at least 60 minutes (or at a maximum of 10 mg/min, whichever was longer)
  - IV cefazolin 75 mg/kg/day divided q8h (± 1 hour) infused over 60 (± 10) minutes
  - Optional IV aztreonam 30 mg/kg q8h (± 1 hour) infused over 60 (± 10) minutes, at any time during IV therapy if an infection involving a Gram-negative pathogen was identified or suspected
- Oral Switch
  - Cephalexin at 25 mg/kg q6h [preferred switch]
  - Clindamycin 10 mg/kg q8h
  - Linezolid [600 mg every 12 hours (q12h) [Cohort 1] or 10 mg/kg q8h [Cohorts 2, 3, and 4])

Additional details regarding the design of Study P903-23 can be found in the Clinical Study Report. A Schedule of Assessments and Procedures can be found in **Appendix 13.3**.

Reviewer comment: *The Sponsor's proposed dose for labeling suggests a modification from the dose used in the ABSSSI Study P903-23 and the CABP Study P903-31.* (b) (4) *. Please refer to the Clinical Pharmacology review by Kunyi Wu, PharmD for details.*

Study Endpoints

- *Safety*

The primary objective of Study P903-23 was to evaluate the safety of ceftaroline fosamil as a treatment for ABSSSI in children.

The primary safety outcome measures included:

1. Adverse events: AEs**,** serious adverse events (SAEs)**,** deaths, and discontinuations due to AEs; cephalosporin class effects and additional AEs
(including, but not limited to, seizures, *Clostridium difficile*-associated diarrhea, allergic reactions, hepatic abnormalities, hemolytic anemia, and changes in renal

function)
2. Laboratory: complete blood count (CBC) with differential, direct Coombs test, and chemistry panel
3. Clinical: vital signs (pulse, blood pressure, respiratory rate, temperature)

Other clinical assessments included body weight measurements and pain scale assessments.

- *Efficacy*

Study P903-23 was not powered for comparative inferential analyses, and there was no primary efficacy endpoint. However, several exploratory endpoints were examined. No hypothesis testing was performed.

Efficacy outcome measures are listed:

1. Clinical response at Study Day 3 in the Modified Intent-to-Treat (MITT) Population
2. Clinical outcome at EOIV, EOT, and TOC in the MITT and Clinically Evaluable (CE) populations
3. Clinical and microbiological outcomes by subject and by baseline pathogen at TOC in the Microbiological Modified Intent-to-Treat (mMITT) and Microbiologically Evaluable (ME) populations
4. Clinical relapse at LFU in the MITT Population
5. Emergent infections in the mMITT Population

Clinical response definitions used in P903-23 were as follows:

- Definition 1: ≥ 20% reduction from baseline in total infection area (length × width)
- Definition 2: Cessation of spread relative to baseline as measured by total infection area
- Definition 3: Cessation of spread relative to baseline as measured by length and width, separately, AND temperature < 37.6°C, irrespective of temperature collection method.

Reviewer Comment: *The exploratory endpoints used definitions similar to those applied to the adult Phase 3 ABSSSI trials for ceftaroline fosamil (P903-06 and P903-07). Definition 1 is consistent with the FDA Guidance for Industry for ABSSSI.*[7] *Definition 3 is the definition of response used in the original NDA application to the FDA for the use of ceftaroline fosamil in adults with ABSSSI.*

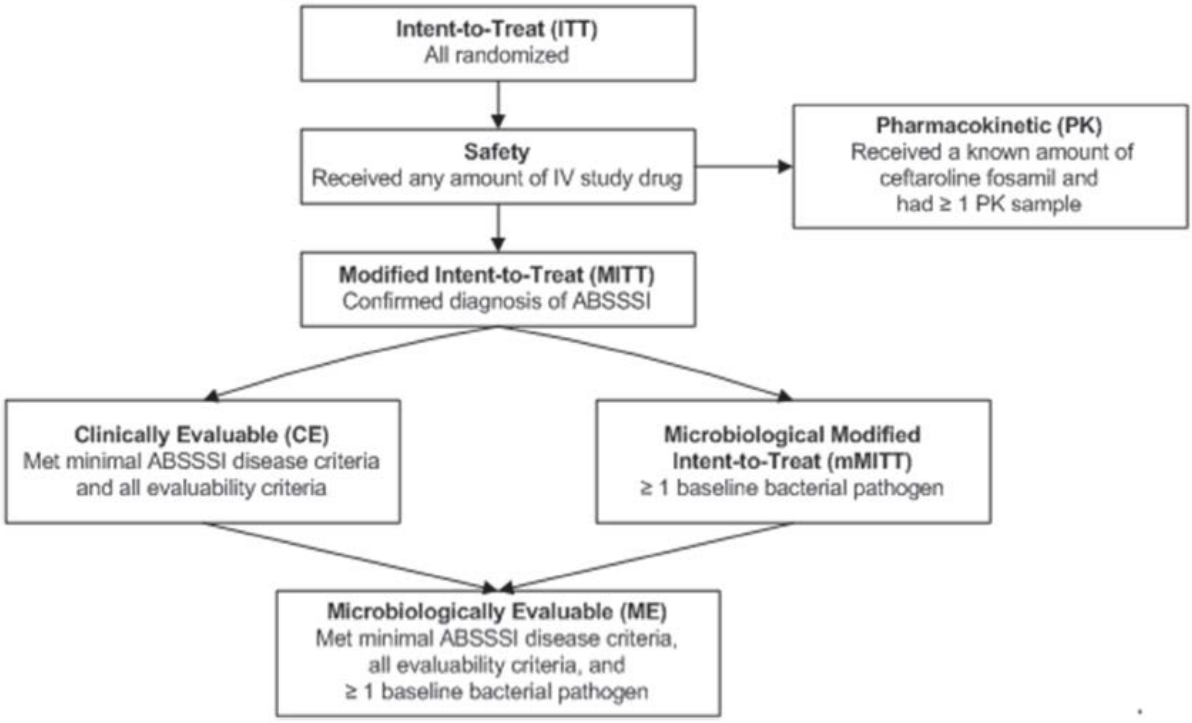
Definitions for clinical and microbiologic outcomes categories at the End-of-Intravenous Study Drug Administration, End-of-Therapy, Test-of-Cure and Late Follow-up are summarized inAppendix 13.4.

Statistical Analysis Plan

Study P903-23 was not powered for comparative inferential analyses, and there was no primary efficacy endpoint. However, several exploratory endpoints were examined. No hypothesis testing was performed. Please refer to the Statistical Review for a detailed evaluation of the Applicant's planned statistical analysis.

Subject Populations are illustrated in **Figure 2**.

Figure 2 Study P903-23 Subject Populations



Source: NDA 200327 Clinical Study Report for P903-23, Figure 9.7.1.1-1, Subject Populations.

No interim efficacy analyses were planned for this study. Analyses by baseline subgroups of interest included sex, region of enrollment, baseline CrCl category, presence of bacteremia, enrollment as a prior treatment failure, and description of infection.

Protocol Amendments

Key details for protocol amendment submissions are summarized in **Appendix 13.3**.

Data Quality and Integrity: Sponsor's Assurance

Data collection used the (b) (4) system ((b) (4)), to which only authorized personnel had access. After all data were entered, source data verified, and all critical queries were resolved, the database was locked (ie, no further changes were possible) and unblinded for analyses.

An audit of the clinical study report was conducted by Cerexa, Inc.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Sponsor sates that Study P903-23 was carried out in compliance with ICH-E6 Good Clinical Practice.

Financial Disclosure

For Study P903-23, Financial Disclosure information could not be obtained from Principal Investigators and Sub-Investigators at Site Number 702 and 804. The Sponsor certifies that they have acted with due diligence to obtain these financial disclosures. Please see **Appendix 13.2** for additional details.

Reviewer Comment: *Sites 702 and 804 enrolled 6 subjects and 1 subject, respectively. All 7 subjects were enrolled in the ceftaroline arm. These 7 subjects represents 7/96 (7.3%) of the Clinically Evaluable Population and 7/107 (6.5%) of the modified intent-to-treat population (MITT) of the ceftaroline fosamil arm in Study P903-23. Because the study is not powered for inferential analyses, and information on safety in the pediatric population can be used, these sites are included in subsequent analyses.*

Patient Disposition

The number and percentage of subjects in each analysis population, as well as the reasons for exclusion from the respective populations by treatment group in the pediatric ABSSSI study, are shown in **Appendix 13.5** . In the two treatment groups, the percentages of subjects, with reasons for exclusion from the various populations, were similar.

The majority of subjects in Study P903-23 completed study drug therapy (ceftaroline 90.9%, comparator 88.7%) (**Appendix 13.5**,). The percentage of subjects who discontinued IV or oral study drug was similar between treatment groups (ceftaroline 9.1%, comparator 11.3%).

The majority of subjects in Study P903-23 completed study (ceftaroline 93.6%, comparator 90.6%). The percentage of subjects who withdrew from the study (ceftaroline 6.4%, comparator 9.4%), as well as associated reasons, was similar between treatment groups.

Protocol Violations/Deviations

In the ceftaroline fosamil arm, two subjects received incorrect study drug. The first subject was randomized to ceftaroline fosamil but received cefazolin instead of ceftaroline fosamil. The second subject received aztreonam in addition to ceftaroline fosamil. Both subjects were retained in the ceftaroline group for efficacy analyses but were excluded from the CE and ME populations.

Efficacy Results – Primary Endpoint

Reviewer comment*: Study P903-23 was not powered for comparative inferential analyses. There was no primary efficacy endpoint. Several exploratory endpoints were examined. The Statistical Reviewer, Daniel Rubin, PhD was able to replicate the efficacy results submitted by the Sponsor. Please refer to Dr. Rubin's review for additional details.*

Efficacy Results – Secondary and other relevant endpoints

Although not powered for efficacy interpretations, clinical response rates at Study Day 3, clinical outcomes at TOC and LFU, as well as microbiological outcomes were similar in the ceftaroline and comparator groups.

Clinical Response at Study Day 3

Clinical response rates at Study Day 3 (MITT Population) were similar in both treatment arms for all three pediatric definitions used (**Table 5**).

Table 5 Clinical Response at Study Day 3 by Treatment Group Overall, Study P903-23—MITT Population.

Response	*Ceftaroline (N = 107) n (%)*	*Comparator (N = 52) n (%)*	*Difference (%)*
Definition 1: ≥ 20% reduction from baseline infection area			
Responder	91 (85.0)	44 (84.6)	0.4
95% CI	(76.9, 91.2)	(71.9, 93.1)	(–10.7, 13.9)
Non-responder	11 (10.3)	4 (7.7)	—
Incomplete data	5 (4.7)	4 (7.7)	—
Definition 2: Cessation of spread measured by total infection area			
Responder	98 (91.6)	47 (90.4)	1.2
95% CI	(84.6, 96.1)	(79.0, 96.8)	(–7.7, 13.0)
Non-responder	4 (3.7)	1 (1.9)	—
Incomplete data	5 (4.7)	4 (7.7)	—
Definition 3: Cessation of spread measured by infection length and width separately, and temperature < 37.6°C			
Responder	86 (80.4)	39 (75.0)	5.4
95% CI	(71.6, 87.4)	(61.1, 86.0)	(–7.8, 20.3)
Non-responder	16 (15.0)	9 (17.3)	—
Incomplete data	5 (4.7)	4 (7.7)	—

Notes: Difference is the ceftaroline treatment group percentage minus comparator group percentage; the CIs for individual groups are calculated using the exact Clopper-Pearson method; the CIs for the difference between treatment groups are calculated using the method of Miettinen and Nurminen without stratification.
The symbol "—" signifies that data are not applicable.
Abbreviations: CI = confidence interval; MITT = Modified Intent-to-Treat.
Source: ABSSSI Module 2.7.3, Table 6.2.2.1-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.2.2.1-1.

Reviewer comment: *Responder rates in the pediatric studies are similar to that observed in the adult studies (**Table 6**).*

Table 6 Clinical Response at Study Day 3 by Treatment Group Overall, Pooled Adult Studies P903-06 and P903-07—MITT Population.

Response	*Pooled Phase 3 Studies (06, 07)*		*Difference (%)*
	Ceftaroline (N = 400) n (%)	*Vancomycin plus aztreonam (N = 397) n (%)*	
Cessation of spread measured by total infection area (Analogous to Pediatric Definition 2)			
Responder	369 (92.3%)	358 (90.2%)	2.1 (–1.9, 6.2)
Cessation of spread measured by infection length and width separately, and temperature < 37.6°C (Analogous to Pediatric Definition 3)			
Responder	296 (74.0%)	263 (66.2%)	7.7 (1.3, 14.0)

Notes: Difference is the ceftaroline treatment group percentage minus comparator group percentage; the CIs for individual groups are calculated using the exact Clopper-Pearson method; the CIs for the difference between treatment groups are calculated using the method of Miettinen and Nurminen without stratification.
Abbreviations: CI = confidence interval; cSSSI = complicated skin and skin structure infection; FDA = Food and Drug Administration; MITT = modified intent-to-treat; NDA = New Drug Application.
Source: cSSSI Exploratory Table 1 (FDA Logic) and cSSSI Exploratory Table 2 (FDA Logic) in the response document submitted to the NDA on 20 September 2010 (Sequence No. 0039).

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.2.2.2-1.

Clinical outcomes at Test of Cure

Clinical cure rates at TOC in the MITT population were 94.4% and 86.5% in children treated with ceftaroline and comparator, respectively, with similar results in the mMITT Population (ceftaroline 94.2%, comparator 81.8%) (**Appendix 13.5; Table 39**.)

Clinical outcomes at Late Follow-Up

Almost all subjects with a clinical cure at TOC also had a clinical cure at LFU (ceftraoline 98.0%, comparator 100.0%) (**Appendix 13.5, Table 41**). In the pooled adult studies (P903-06 and P903-07), approximately 1% of subjects with a clinical cure at TOC had a clinical relapse at LFU.

Additional details including demographic characteristics, other baseline characteristics (e.g., disease characteristics, important concomitant drugs), and Additional Sub-group Analyses conducted on the individual trial can be found in **Appendix 13.5**.

Reviewer comment: *Exploratory subgroup analyses by age, sex and baseline pathogen were conducted to understand efficacy trends for response rates at Study Day 3 and cure rates at Test-of-Cure in the pediatric population. Small sample sizes preclude making conclusions for any subgroup efficacy analyses. Microbiologic response is not described because this was based on clinical outcomes, and eradication was presumed for each pathogen since post-baseline pathogens were not identified.*

6.2. Study P903-31: A Multicenter, Randomized, Observer Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone in Pediatric Subjects With Community-acquired Bacterial Pneumonia Requiring Hospitalization (DC3720C00007)

6.2.1. Study Design

Overview and Objective

Study P903-31 aimed to evaluate the safety, efficacy, and PK of intravenous (IV) ceftaroline versus IV comparator (ceftriaxone) in pediatric subjects from the ages of 2 months to < 18 years with CABP requiring hospitalization. The trial primarily assessed safety and was not powered for formal efficacy evaluations.

Primary Objective
To evaluate the safety and tolerability of ceftaroline versus ceftriaxone in pediatric subjects, ages 2 months to < 18 years, with community-acquired bacterial pneumonia (CABP) requiring hospitalization

Secondary Objective
1. To evaluate the efficacy of ceftaroline versus ceftriaxone in pediatric subjects with CABP requiring hospitalization
2. To evaluate the pharmacokinetics (PK) of ceftaroline in pediatric subjects ages 2 months to < 18 years with CABP requiring hospitalization

Trial Design

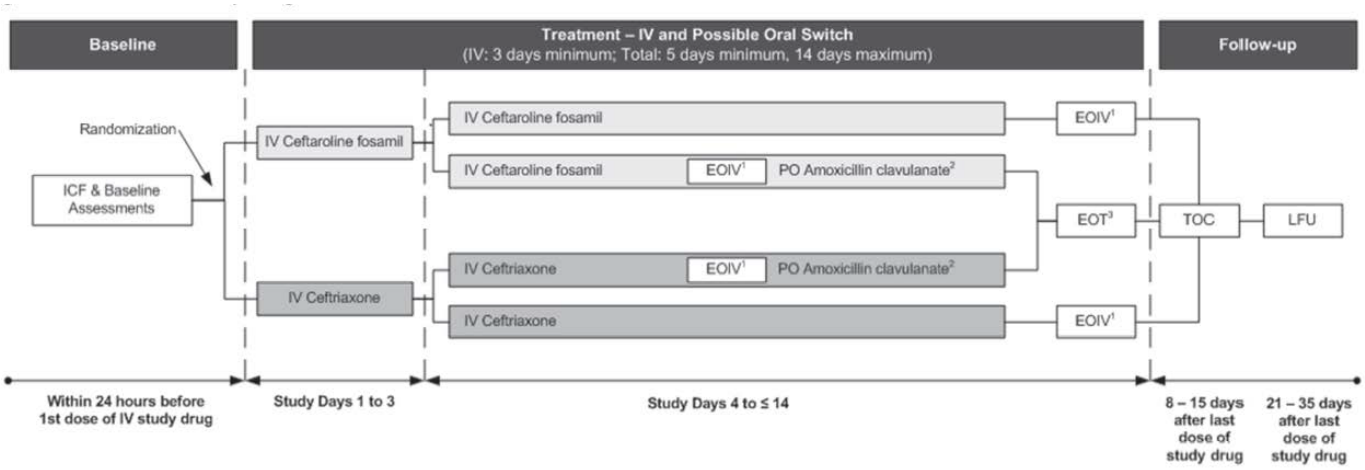
- *Basic study design:*
  Study P903-31 was a Phase 2/3 multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, PK, and efficacy of ceftaroline versus ceftriaxone in pediatric subjects aged 2 months to < 18 years with CABP requiring hospitalization (**Figure 3**). Subjects were stratified by age cohort and region and were

randomly assigned to treatment in a 3:1 ratio, ceftaroline fosamil to ceftriaxone.

There were four cohorts of descending age:

- Cohort 1: children from 12 years to < 18 years
- Cohort 2: children from 6 years to < 12 years
- Cohort 3: children from 24 months to < 6 years
- Cohort 4: young infants/toddlers from 2 months to < 24 months

Figure 3 Study P903-31: Study Design



Abbreviations: EOIV = End-of-Intravenous Study Drug Therapy; EOT = End-of-Therapy; ICF = informed consent form; IV = intravenous; LFU = Late Follow-up; PO = by mouth; TOC = Test-of-Cure.
[1] EOIV = within 24 hours after the last dose of IV study drug and, if applicable, before switch to PO study drug.
[2] PO switch to amoxicillin clavulanate was allowed on or after Study Day 4 per protocol.
[3] EOT = within 48 hours after the last dose of PO study drug.

Source: NDA 200327 Clinical Study Report for P903-31, Figure 9.1-1, Study Design.

On, or after Study Day 4, subjects meeting pre-defined criteria could switch from IV to open label oral study drug.

Study treatments were as follows.

- Ceftaroline fosamil
  IV ceftaroline fosamil infused over 60 (± 10) minutes every 8 hours (q8h) (± 1 hour) as follows:
  - Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg
  - Children < 6 months: ceftaroline fosamil 8 mg/kg
- Comparator
  - IV ceftriaxone 75 mg/kg/day, up to a maximum of 4 g/day, divided q12h (± 1 hour) infused over 30 (± 10) minutes
- Oral Switch

- Amoxicillin clavulanate 90 mg/kg/day divided equally every 12 hours

Additional details regarding the design of Study P903-31 can be found in the Clinical Study Report. A Schedule of Assessments and Procedures can be found in **Appendix 13.6.**

Study Endpoints

- Safety

The primary objective of Study P903-31 was to evaluate the safety of ceftaroline fosamil as a treatment for CABP in hospitalized children.

The primary safety outcome measures included:

1. Adverse events: AEs**,** serious adverse events (SAEs)**,** deaths, and discontinuations due to AEs; cephalosporin class effects and additional AEs (including, but not limited to, seizures, *Clostridium difficile*-associated diarrhea, allergic reactions, hepatic abnormalities, hemolytic anemia, and changes in renal function)
2. Laboratory: complete blood count (CBC) with differential, direct Coombs test, and chemistry panel
3. Clinical: vital signs (pulse, blood pressure, respiratory rate, temperature) and oxygen saturation

- Efficacy

Study P903-31 was not powered for comparative inferential analyses, and there was no primary efficacy endpoint. However, several exploratory endpoints were examined. No hypothesis testing was performed.

Efficacy outcome measures are listed:

1. Clinical response at Study Day 4 in the Modified Intent-to-Treat (MITT) Population and the Microbiologic Modified Intent-to-Treat (mMITT) populations
2. Clinical stability at Study Day 4 by subject and by baseline pathogen in the MITT and mMITT populations
3. Clinical outcome at EOIV, EOT, and TOC in the MITT and Clinically Evaluable (CE) populations
4. Clinical and microbiological outcomes by subject and by baseline pathogen at TOC in the Microbiological Modified Intent-to-Treat (mMITT) and Microbiologically Evaluable (ME) populations
5. Clinical relapse at LFU in the MITT Population
6. Emergent infections in the mMITT Population

- Clinical Response at Study Day 4:
  Clinical response at Study Day 4 was programmatically derived by the Sponsor in

a blinded manner. Clinical response was defined as improvement in at least two and worsening of none of the following symptoms compared to baseline:

1. Cough
2. Dyspnea
3. Sputum production
4. Chest pain
5. Chills or rigors
6. Feeling of warmth/feverish
7. Exercise intolerance or lethargy

- Clinical Stability at Study Day 4:
  Clinical stability at Study Day 4 was programmatically derived by the Sponsor in a blinded manner and was defined by having met all of the following criteria:
  1. Afebrile (temperature ≤ 38.0°C by any measurement method)
  2. Age-appropriate normal pulse and respiratory rates
  3. Oxygen saturation ≥ 92% on room air
  4. Worsening of none of the following symptoms relative to baseline: cough, dyspnea, chest pain, sputum production, chills or rigors, feeling of warmth / feverish, and exercise intolerance or lethargy

Reviewer Comment: *The exploratory endpoints used definitions similar to those applied to the adult Phase 3 CABP trials for ceftaroline fosamil (P903-08 and P903-09) and are consistent with the FDA Guidance for Industry for CABP.*[8]

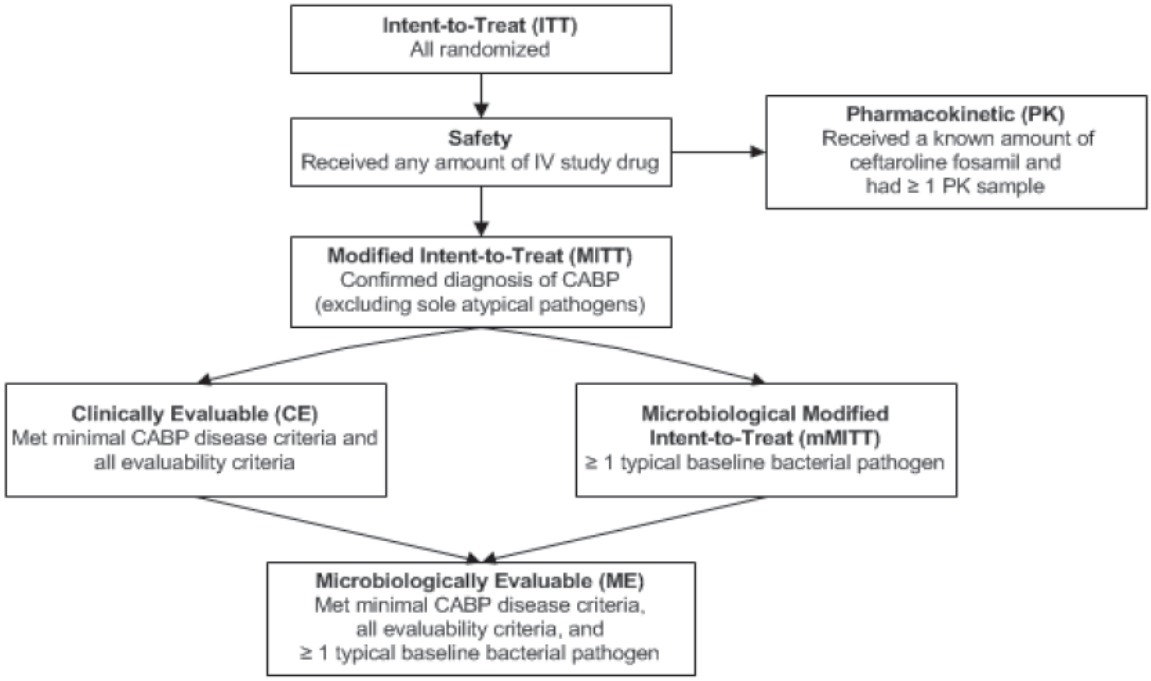
Definitions for clinical and microbiologic outcomes at the End-of-Intravenous Study Drug Administration, End-of-Therapy, Test-of-Cure and Late Follow-up are summarized in **Appendix 13.7.**

Statistical Analysis Plan

Study P903-31 was not powered for comparative inferential analyses, and there was no primary efficacy endpoint. However, several exploratory endpoints were examined. No hypothesis testing was performed. Please refer to the Statistical Review for a detailed evaluation of the Applicant's planned statistical analysis.

Subject Populations are illustrated in Figure 4.

Figure 4 Study P903-31 Subject Populations



Abbreviations: CABP = community-acquired bacterial pneumonia; IV = intravenous.

Source: NDA 200327 Clinical Study Report for P903-31, Figure 9.7.1.1-1, Subject Populations.

No interim efficacy analyses were planned for this study. Efficacy results were analyzed by baseline subgroups of interest including sex, region of enrollment, disease markers as well as age cohorts.

Data Quality and Integrity: Sponsor's Assurance

Data collection used the [redacted] (b) (4) system [redacted] (b) (4)), to which only authorized personnel had access. After all data were entered, source data verified, and all critical queries were resolved, the database was locked (ie, no further changes were possible) and unblinded for analyses.

An audit of the clinical study report was conducted by Cerexa, Inc.

6.2.2. Study Results

Study results for Study P903-31 are discussed in parallel with Study P903-24, the pediatric complicated CABP study. Please refer to **Section 6.3.2** for study results for Study P903-31.

6.3. Study P903-24: A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone Plus Vancomycin in Pediatric Subjects with Complicated Community-acquired Bacterial Pneumonia

6.3.1. Study Design

Overview and Objective

Study P903-24 aimed to evaluate the safety, efficacy, and PK of intravenous (IV) ceftaroline versus IV comparator (ceftriaxone plus vancomycin) in pediatric subjects from the ages of 2 months to < 18 years with complicated CABP. The trial primarily assessed safety and was not powered for formal efficacy evaluations.

Primary Objective
To evaluate the safety and tolerability of ceftaroline versus ceftriaxone plus vancomycin in pediatric subjects ages 2 months to < 18 years with complicated community-acquired bacterial pneumonia (CABP)

Secondary Objective
1. To evaluate the efficacy of ceftaroline versus ceftriaxone plus vancomycin in pediatric subjects with complicated CABP at high risk of infection due to methicillin-resistant *Staphylococcus aureus* (MRSA)
2. To evaluate the pharmacokinetics (PK) of ceftaroline in pediatric subjects ages 2 months to < 18 years with complicated CABP

Trial Design

Key differences in study designs and efficacy assessments between studies P903-31 and P903-24 are described in **Table 7**. Details for Study P903-24 are described in this section.

Table 7 Key Differences in Study Designs and Efficacy Assessments Between Studies P903-31 and P903-24

Criterion	P903-31	P903-24
Eligibility criteria	Subjects must have had presence of CABP requiring hospitalization and IV antibacterial therapy Subjects with a confirmed or suspected infection with a pathogen known to be resistant to ceftriaxone (eg, *Pseudomonas aeruginosa*, MRSA) were excluded Subjects with risk factors for MRSA infection who had a predominance of Gram-positive cocci in clusters on sputum Gram stain were excluded	Subjects must have had presence of complicated CABP that warranted 3 days of initial hospitalization and a minimum of 3 days of IV antibacterial therapy and a minimum of 5 days, but no more than 21 days total of study therapy (IV and oral combined) Subjects must have had 1 of the following indicators of complicated CABP: empyema, pulmonary abscess, necrotizing pneumonia, pneumatocele, pleural effusion, Gram-positive cocci in clusters from respiratory specimen, requirement for positive pressure assisted ventilation, previous influenza-like illness or documented influenza infection, or severe CABP defined as requiring treatment in an intensive care unit
Dose	Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg infused over 60 minutes q8h Children < 6 months: ceftaroline fosamil 8 mg/kg infused over 60 minutes q8h	Children ≥ 6 months: ceftaroline fosamil 15 mg/kg for subjects weighing ≤ 40 kg or 600 mg for subjects weighing > 40 kg infused over 120 minutes q8h Children < 6 months: ceftaroline fosamil 10 mg/kg infused over 120 minutes q8h
Treatment duration	Up to 14 days	Up to 21 days
Comparator	Ceftriaxone	Ceftriaxone + vancomycin
Switch to oral antibiotics	Amoxicillin clavulanate	Amoxicillin clavulanate (preferred switch), clindamycin, or linezolid
Clinical outcome definition at EOIV	"Indeterminate" defined as extenuating circumstances that precluded classification as a cure, improvement, or failure	"Indeterminate" defined as extenuating circumstances that precluded classification as a cure or failure
Other	Not applicable	Designed to enrich for subjects at risk for CABP due to MRSA

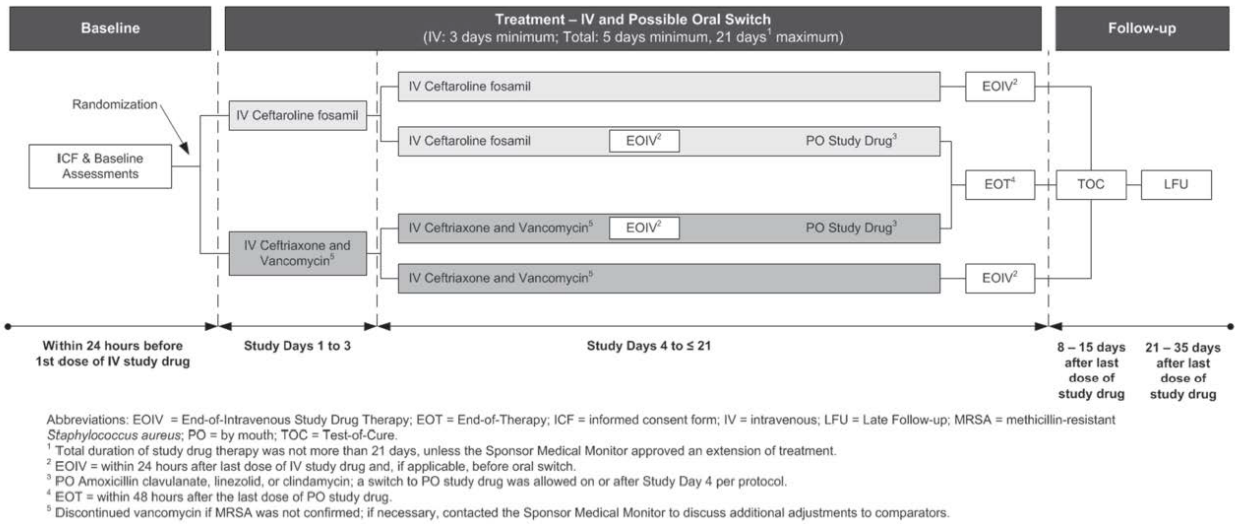
Abbreviations: CABP = community-acquired bacterial pneumonia; EOIV = End-of-Intravenous Study Drug; IV = intravenous; MRSA = methicillin-resistant *S. aureus*; q8h = every 8 hours

Source: NDA 200327 Module 2.5 Clinical Overview, Table 4.2.1-1.

- *Basic study design:*
  Study P903-24 was a Phase 4, multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, PK, and efficacy of intravenous (IV) ceftaroline fosamil versus IV ceftriaxone plus IV vancomycin (referred to as comparators) in pediatric subjects aged 2 months to < 18 years with complicated CABP, which was designed to enrich for subjects at risk for infection due to MRSA (**Figure 5**). Subjects were stratified by age cohort and region and were randomly assigned to treatment in a 3:1 ratio, ceftaroline fosamil to ceftriaxone.

  There were four cohorts of descending age:
    - Cohort 1: children from 12 years to < 18 years
    - Cohort 2: children from 6 years to < 12 years
    - Cohort 3: children from 24 months to < 6 years
    - Cohort 4: young infants/toddlers from 2 months to < 24 months

Figure 5 Study P903-24: Study Design



Abbreviations: EOIV = End-of-Intravenous Study Drug Therapy; EOT = End-of-Therapy; ICF = informed consent form; IV = intravenous; LFU = Late Follow-up; MRSA = methicillin-resistant *Staphylococcus aureus*; PO = by mouth; TOC = Test-of-Cure.
[1] Total duration of study drug therapy was not more than 21 days, unless the Sponsor Medical Monitor approved an extension of treatment.
[2] EOIV = within 24 hours after last dose of IV study drug and, if applicable, before oral switch.
[3] PO Amoxicillin clavulanate, linezolid, or clindamycin; a switch to PO study drug was allowed on or after Study Day 4 per protocol.
[4] EOT = within 48 hours after the last dose of PO study drug.
[5] Discontinued vancomycin if MRSA was not confirmed; if necessary, contacted the Sponsor Medical Monitor to discuss additional adjustments to comparators.

Source: NDA 200327 Clinical Study Report for P903-24, Figure 9.1-1, Study Design.

On, or after Study Day 4, subjects meeting pre-defined criteria could switch from IV to open label oral study drug.

Study treatments included the following

- Ceftaroline fosamil
  IV ceftaroline fosamil infused over 120 (± 10) minutes every 8 hours (q8h) (± 1 hour) as follows:
    - Children ≥ 6 months: ceftaroline fosamil 15 mg/kg for subjects weighing ≤ 40 kg or 600 mg for subjects weighing > 40 kg

- Children < 6 months: ceftaroline fosamil 10 mg/kg

- Comparator
  - IV ceftriaxone 75 mg/kg/day, up to a maximum of 4 g/day, divided q12h (± 2 hours) infused over 30 (± 10) minutes

  - Vancomycin as initial empiric therapy of 15 mg/kg q6h (± 1 hour), infused over at least 60 minutes (or at a maximum of 10 mg/min, whichever was longer)

    Vancomycin may have been discontinued on or after Study Day 4 (after 72 hours of IV study drug) if MRSA, PRSP, or PISP was not confirmed or suspected. Because the subjects in this study were at risk for infection due to MRSA, Investigators were advised to carefully weigh the risk of discontinuing vancomycin. Vancomycin trough levels at study centers where trough levels were measured as standard of care for vancomycin-treated subjects, were to be recorded on the appropriate screens(s) of the eCRF.

- Oral Switch
  - Amoxicillin clavulanate 90 mg/kg/day divided equally every 12 hours
  - Clindamycin at 13 mg/kg/dose q8h
  - Linezolid 600 mg q12h (Cohort 1) or 10 mg/kg q8h (Cohorts 2, 3, and 4)

Additional details regarding the design of Study P903-24 can be found in the Clinical Study Report. A Schedule of Assessments and Procedures can be found in **Appendix 13.8**.

Study Endpoints

- Safety
  The primary objective of Study P903-24 was to evaluate the safety of ceftaroline fosamil as a treatment for complicated CABP in children. The primary safety outcome measures were similar to Study P903-31, described previously.

- Efficacy
  Study P903-24 was not powered for comparative inferential analyses, and there was no primary efficacy endpoint. However, several exploratory endpoints were examined. No hypothesis testing was performed. Efficacy outcome measures were similar to Study P903-31, described previously.

  Clinical Response at Study Day 4 and Clinical Stability at Study Day 4 were defined the

same as in Study P903-31, described previously.

A sparse PK sampling schedule was used for PK data acquisition and analysis.

Statistical Analysis Plan

Study P903-24 was not powered for comparative inferential analyses, and there was no primary efficacy endpoint. However, several exploratory endpoints were examined. No hypothesis testing was performed. Please refer to the Statistical Review for a detailed evaluation of the Applicant's planned statistical analysis.

Subject Populations were defined similar to Study P903-31, described previously.

No interim efficacy analyses were planned for this study. No subgroup analyses were performed due to small sample size.

Data Quality and Integrity: Sponsor's Assurance

Data collection used the (b) (4) system ((b) (4)), to which only authorized personnel had access. After all data were entered, source data verified, and all critical queries were resolved, the database was locked (ie, no further changes were possible) and unblinded for analyses.

An audit of the clinical study report was conducted by Cerexa, Inc.

6.3.2. Study Results

Compliance with Good Clinical Practices

The Sponsor states that Study P903-31 and Study P903-24 was carried out in compliance with ICH-E6 Good Clinical Practice.

Financial Disclosure

For Study P903-31 and Study P903-24, there were no Principal Investigators and Sub-Investigators with disclosable financial arrangements.

Patient Disposition

The number and percentage of subjects in each analysis population, as well as the reasons for exclusion from the respective populations by treatment group in the pediatric CABP studies, are shown in **Appendix 13.9,** .

The percentage of subjects in all of the populations was similar between the ceftaroline and the ceftriaxone treatment groups in Study P903-31. Isolation of a sole atypical pathogen was the most common reason for exclusion from the MITT Population in both treatment groups.

In Study P903-24, two subjects, 1 in each treatment group, were excluded from the MITT Population because of the presence of a sole atypical pathogen.

The majority of subjects in Study P903-31 and P903-24 completed study drug therapy ([P903-31; ceftaroline 91.0%, comparator 89.7%],[P903-24; ceftaroline 90.0%, comparator 100.0%]) (**Appendix 13.9,**). The percentage of subjects who discontinued IV or oral study drug was similar between treatment groups in Study P903-31 ([P903-31; ceftaroline 9.0%, comparator 10.3%],[P903-24; ceftaroline 10.0%, comparator 0%]). Sample sizes in Study P903-24 were too small to draw any conclusions.

The majority of subjects in Study P903-31 completed the study and all subjects in Study P903-24 completed the study ([P903-31; ceftaroline 95.1%, comparator 97.4%],[P903-24; ceftaroline 100.0%, comparator 100.0%]) (**Appendix 13.9,**). In Study P903-31, there was no discernible pattern regarding the reasons for premature withdrawal from the study.

Efficacy Results - Primary Endpoint

Reviewer comment*: Study P903-31 and Study P903-24 were not powered for comparative inferential analyses. There was no primary efficacy endpoint. Several exploratory endpoints were examined. The Statistical Reviewer, Daniel Rubin, PhD was able to replicate the efficacy results submitted by the Sponsor. Please refer to Dr. Rubin's review for additional details.*

Efficacy Results - Secondary and other relevant endpoints

Although not powered for efficacy interpretations, results from Study P903-31, suggest that clinical response and stability at Study Day 4, as well as Clinical Outcomes at Test-of-Cure were similar in the ceftaroline fosamil and comparator arms. Sample sizes are too small in Study P903-24 for any conclusions to be made.

Clinical Response and Stability at Study Day 4

In Study P903-31, the clinical response rates at Study Day 4 were similar between the ceftaroline fosamil and ceftriaxone treatment groups in the MITT Population (69.2% and 66.7%, respectively) (**Table 8**). In addition, the percentage of subjects with clinical stability was similar in the ceftaroline fosamil and ceftriaxone treatment groups (34.6% and 36.1%, respectively) (**Table 8**).

In Study P903-24, the percentage of responders in the MITT population was greater than 50% in the ceftaroline fosamil and ceftriaxone treatment groups (51.7% and 66.7%, respectively) at Study Day 4 (**Table 8**). In addition, clinical stability was reached by 20.7% and 22.2% of subjects in the ceftaroline and comparator groups, respectively (**Table 8**).

Table 8 Clinical Response and Stability at Study Day 4—MITT and mMITT Populations.

Response/Stability	*P903-31*			*P903-24*		
	Ceftaroline n (%)	*Ceftriaxone n (%)*	*Difference (%)*	*Ceftaroline n (%)*	*Comparator n (%)*	*Difference (%)*
MITT Population						
Clinical response						
N	107	36	—	29	9	—
Responder	74 (69.2)	24 (66.7)	2.5	15 (51.7)	6 (66.7)	–14.9
95% CI	(59.5, 77.7)	(49.0, 81.4)	(–13.9, 20.9)	—	—	(–44.6, 22.0)
Non-Responder	24 (22.4)	11 (30.6)	—	11 (37.9)	3 (33.3)	—
Incomplete Data	9 (8.4)	1 (2.8)	—	3 (10.3)	0	—
Clinical stability						
N	107	36	—	29	9	—
Stability	37 (34.6)	13 (36.1)	–1.5	6 (20.7)	2 (22.2)	–1.5
95% CI	(25.6, 44.4)	(20.8, 53.8)	(–20.1, 15.3)	—	—	(–37.2, 23.8)
No stability	60 (56.1)	23 (63.9)	—	22 (75.9)	7 (77.8)	—
Incomplete Data	10 (9.3)	0	—	1 (3.4)	0	—
mMITT Population						
Clinical response						
N	24	9	—	15	3	—
Responder	14 (58.3)	7 (77.8)	–19.4	8 (53.3)	3 (100.0)	–46.7
95% CI	(36.6, 77.9)	(40.0, 97.2)	(–47.2, 18.8)	—	—	(–70.4, 16.6)
Non-Responder	7 (29.2)	1 (11.1)	—	5 (33.3)	0	—
Incomplete Data	3 (12.5)	1 (11.1)	—	2 (13.3)	0	—
Clinical stability						
N	24	9	—	15	3	—
Stability	5 (20.8)	1 (11.1)	9.7	2 (13.3)	0	13.3
95% CI	(7.1, 42.2)	(0.3, 48.2)	(–26.0, 33.3)	—	—	(–46.5, 38.7)
No stability	15 (62.5)	8 (88.9)	—	12 (80)	3(100.0)	—
Incomplete Data	4 (16.7)	0	—	1 (6.7)	0	—

Notes: Difference is the ceftaroline treatment group percentage minus the ceftriaxone group percentage; the CIs for individual groups were calculated using the exact Clopper-Pearson method; the CIs for the difference between treatment groups were calculated using the method of Miettinen and Nurminen without stratification.
Clinical stability at Study Day 4 is defined as meeting all of the following criteria: (1) Afebrile (temperature ≤ 38.0°C), (2) Age-appropriate normal pulse and respiratory rates, as defined in Table 10.2-1 of the SAP, (3) Oxygen saturation ≥ 92% on room air, (4) Worsening of none of the following symptoms relative to baseline: cough, dyspnea, chest pain, sputum production, chills or rigors, feeling feverish, and exercise intolerance or lethargy.
The symbol "—" signifies that data are not applicable.
Abbreviations: CI = confidence interval; MITT = Modified Intent-to-Treat; mMITT = microbiological Modified Intent-to-Treat; SAP = Statistical Analysis Plan.
Source: CABP Module 2.7.3, Table 6.2.2.1-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.2.2.1-1.

In the pooled adult CABP studies, P903-08 and P903-09, an FDA-defined mMITT population, which was a subset of the mMITTE population, was used in the analysis of clinical response at Study Day 4. Response rates were similar in the ceftaroline fosamil and ceftriazone arms (70.2% and 58.8%, respectively) (**Table 9**).

Table 9 Clinical Response at Study Day 4, Pooled Phase 3 Adult Studies — FDA Defined mMITT Population.

Population/Clinical Response	*Pooled Phase 3 Studies (08, 09)*	
	Ceftaroline n (%)	*Ceftriaxone n (%)*
Response at Study Day 4		
N	151	153
Responder	106 (70.2)	90 (58.8)
Non-responder	45 (29.8)	63 (41.2)
Crude Difference	11.4	—
Weighted Difference (95% CI)	11.4 (0.6, 21.9)	—

Notes: Crude Difference = Difference in response rates (ceftaroline treatment group minus Comparator treatment group).
Weight Difference = Weighted Difference (stratified by study) in response rates (ceftaroline treatment group minus Comparator treatment group).
The symbol "—" signifies that data are not applicable.
Abbreviations:CI = confidence interval; FDA = Food and Drug Administration; mMITT = microbiological modified intent-to-treat; NDA = New Drug Application.
Source: Table 1 in the response document submitted to the NDA on 20 July 2010 (Sequence No. 0025).

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.2.2.2-1.

Reviewer comment: *Clinical response at Study Day 4 in the pediatric CABP studies show a similar trend as what was observed in the adult studies.*

Clinical Outcomes at Test-of-Cure

In Study P903-31, clinical outcomes at TOC were similar between the ceftaroline fosamil and comparator groups in the MITT Population (87.9% and 88.9%, respectively) (**Appendix 13.9,**). In addition, the clinical cure rates at the TOC visit in the mMITT Population were similar between treatment groups (79.2% and 77.8% for the ceftaroline and comparator groups, respectively).

In Study P903-24, clinical cure rates at TOC were similar between the ceftaroline fosamil and comparator groups in the MITT (89.7% and 100%, respectively) and mMITT (86.7% and 100%, respectively) populations (**Appendix 13.9,**); however, the number of subjects within both treatment groups was small.

In the pooled Phase 3 adult CABP studies, the clinical cure rate at TOC in the MITTE Population was similar in both treatment arms (82.6% in the ceftaroline group compared with 76.6% in the ceftriaxone group) (**Appendix 13.9,**). In the mMITTE Population, the clinical cure rate was 83.6% in the ceftaroline group and 75.0% in the ceftriaxone group.

Reviewer comment: *Clinical response at Test of Cure in the pediatric CABP studies show a similar trend as what was observed in the adult studies.*

In both Study P903-31 and Study P903-24, no subject had a clinical relapse at the LFU visit. This trend was similar to the pooled Phase 3 adult CABP studies where the rate of relapse was similar and low for both treatment groups (ceftaroline, 8/479 [1.7%]; ceftriaxone 5/439 [1.1%]).

Additional details including demographic characteristics, other baseline characteristics (e.g., disease characteristics, important concomitant drugs), and Additional Sub-group Analyses conducted on the individual trial can be found in **Appendix 13.9**.

Reviewer comment: *Exploratory subgroup analyses by age, sex and baseline pathogen were conducted to understand efficacy trends for clinical response and stability at Study Day 4 and cure rates at Test-of-Cure in the pediatric population. Small sample sizes preclude making conclusions for any subgroup efficacy analyses. Microbiologic response is not described because this was based on clinical outcomes, and eradication was presumed for each pathogen since post-baseline pathogens were not identified.*

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. **Primary Endpoints**

The pediatric ABSSSI Study 903-23 and pediatric CABP studies (Study P903-31 and Study P903-24) were not powered for comparative inferential analyses. There was no primary efficacy endpoint.

7.1.2. Secondary and Other Endpoints

Several exploratory endpoints were examined in the pediatric ABSSSI Study 903-23 and pediatric CABP studies (Study P903-31 and Study P903-24). Please refer to **Section 6.1.2** and **Section 6.3.2** for a discussion on the assessment of efficacy trends observed in the pediatric studies compared to corresponding adult Phase 3 trials.

7.1.3. Subpopulations

This section is not applicable for the current submission.

7.1.4. Dose and Dose-Response

PK/PD simulations demonstrated that the proposed dose regimen results in ceftaroline C_{max} and AUC values that more closely match values in adult patients dosed with 600 mg q12h ceftaroline fosamil.

The proposed dose of ceftaroline fosamil for patients < 18 years with normal renal function or mild renal impairment (ie, CrCl > 50 mL/min/1.73 m2), for both ABSSSI and CABP, is:

- Children 2 to < 24 months: 8 mg/kg (over 5 to 60 minutes) q8h
- Children 24 months to < 18 years and ≤ 33 kg: 12 mg/kg (over 5 to 60 minutes) q8h
- Children 24 months to < 18 years and > 33 kg: 400 mg (over 5 to 60 minutes) q8h

Reviewer comment: *The proposed dose suggests a modification from the dose used in the ABSSSI Study P903-23 and the CABP Study P903-31 and is acceptable.* (b) (4) *. Please refer to the Clinical Pharmacology review by Kunyi Wu, PharmD for details.*

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Ceftaroline fosamil is intended for short term use for the treatment of ABSSSI and CABP. A response to treatement was noted with ceftaroline fosamil on Day 3 for ABSSSI and Day 4 for CABP. No patients relapsed in the follow-up phase.

7.2. Additional Efficacy Considerations

This section is not applicable for the current submission.

7.3. Integrated Assessment of Effectiveness

The integrated assessment of effectiveness is summarized by indication, ABSSSI and CABP, for the pediatric population.

Acute Bacterial Skin and Skin structure Infection Indication

Efficacy results from Study P903-23 provide supportive data to expand the adult indication of ABSSSI to the pediatric population (2 months to less than 18 years).

Study P903-23, "A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Ceftaroline Versus Comparator in Pediatric Subjects With Acute Bacterial Skin and Skin Structure Infections (D3720C00004)", was not powered for comparative inferential analyses. There was no primary efficacy endpoint. Several exploratory endpoints were examined.

Clinical response was similar for ceftaroline- and comparator-treated (i.e. vancomycin or cefazolin) subjects in the MITT population of study P903-23. Furthermore, clinical response at Study Day 3 and at TOC was comparable in the pediatric and adult studies (**Table 10**). In Study P903-23, no subject had a relapse at LFU in either treatment arm. Subgroup analyses in Study P903-23 showed similar clinical response rates at Study Day 3 and similar cure rates at Test-of-Cure across all 4 age cohorts; however the small sample sizes preclude definitive conclusions.

Table 10 Clinical Response Rates in Pediatric and Adult ABSSSI Studies at Study Day 3 and Test-of-Cure – MITT population.

	Pediatric (Study P903-23)		Adult (Studies P903-06 and P903-07)	
	Ceftaroline fosamil n (%)	Comparator n (%)	Ceftaroline fosamil n (%)	Comparator n (%)
Study Day 3	N=107	N=52	N=400	N=397
Definition 1: ≥ 20% reduction in infection area from baseline	91 (85.0%)	44 (84.6%)	No analogous definition analyzed in adults.	
Definition 2: Cessation of spread by total infection area	98 (91.6%)	47 (90.4%)	369 (92.3%)	358 (90.2%)
Definition 3: Cessation of spread by infection length and width separately and by temperature < 37.6°C	86 (80.4%)	39 (75.0%)	296 (74.0%)	263 (66.2%)
Test of Cure	N=107	N=52	N=693	N=685
Clinical Cure	101 (94.4%)	45 (86.5%)	595 (85.9%)	586 (85.5%)

Community Acquired Bacterial Pneumonia Indication

Efficacy results from Study P903-31 and Study P903-24 provide supportive data to expand the adult indication of CABP to the pediatric population (2 months to less than 18 years).

The Sponsor combined results from two studies to support efficacy for the CABP indication.

- Study P903-31, "A Multicenter, Randomized, Observer Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone in Pediatric Subjects With Community-acquired Bacterial Pneumonia Requiring Hospitalization (DC3720C00007)"
- Study P903-24, " A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone Plus Vancomycin in Pediatric Subjects with Complicated Community-acquired Bacterial Pneumonia"

Study P903-31 and Study P903-24 were not powered for comparative inferential analyses.

There was no primary efficacy endpoint. Several exploratory endpoints were examined.

For both Study P903-31 and Study P903-24, clinical response rates were similar for ceftaroline- and comparator-treated (i.e. ceftriaxone in Study P903-31 or ceftriaxone plus vancomycin in Study P903-24) subjects in the MITT population. Furthermore, clinical response at Study Day 4, as well as TOC, was comparable in the pediatric and adult studies (**Table 11**). In Study P903-31 and P903-24, no subject had a relapse at LFU in either treatment arm. Subgroup analyses in Study P903-31 suggest similar clinical response and stability rates at Study Day 4 and similar cure rates at Test-of-Cure across all 4 age cohorts; however the small sample sizes preclude definitive conclusions. The Sponsor is not seeking approval for the higher dose used in Study P903-24 because a dose of 600 mg IV q8h is not approved in adults.

Table 11 Clinical Response Rates in Pediatric and Adult CABP Studies at Study Day 4 and Test-of-Cure – MITT population.

	Pediatric (Study P903-31)		**Pediatric (Study P903-24)**		**Adult (Studies P903-08 and P903-09)**	
	Ceftaroline fosamil n (%)	Comparator n (%)	Ceftaroline fosamil n (%)	Comparator n (%)	Ceftaroline fosamil n (%)	Comparator n (%)
Study Day 4[1]	N=107	N=36	N=29	N=9	N=151	N=153
Responder	74 (69.2%)	24 (66.7%)	15 (51.7%)	6 (66.7%)	106 (70.2%)	90 (58.8%)
Stability	37 (34.6%)	13 (36.1%)	6 (20.7%)	2 (22.2%)	Not evaluated in adult studies.	
Test of Cure[2]	N=107	N=36	N=29	N=9	N=580	N=573
Clinical Cure	94 (87.9%)	32 (88.9%)	26 (89.7%)	9 (100%)	479 (82.6%)	439 (76.6%)

[1]MITT (modified intent to treat) population used for pediatric studies, mMITT (FDA defined microbiological modified intent to treat) population used for adult studies.
[2]MITT (modified intent to treat) population used for pediatric studies, MITTE (modified intent to treat efficacy) population used for adult studies.

8 Review of Safety

8.1. Safety Review Approach

A tabular listing of completed studies relevant to this submission is provided in **Section 5.1.** The Sponsor completed 5 clinical studies in their pediatric development program for ceftaroline fosamil (ABSSSI [P903-23], CABP [P903-31 and P903-24], and PK [P903-15 and P903-21]).

The safety review describes results for the active-controlled studies in the following manner: study P903-23 alone (ABSSSI indication), P903-31 and P903-24 combined (CABP indication) and studies P903-23, P903-31 and P903-24 pooled. The safety results for the PK studies, P903-21 and P903-15, were pooled and are described separately. Comparisons with safety data in adults are made, as needed.

***Reviewer comment**: The clinical reviewer conducted safety analyses of the primary data and obtained the same results as those provided by the Sponsor. Hence, where applicable, tables generated by the Sponsor are used in the review.*

While pooling allows for a larger safety database, this approach has a couple key limitations. First, the incidence of adverse events may vary by indication which would not be evident in a pooled analysis. In addition, the impact on the observed incidence of adverse events when studies with different designs (i.e. randomization of 3:1 and 2:1, indications, dosing and/or comparator, etc.) are pooled for safety analyses is not clear. Cumulative AE proportions (weighted methodology accounting for different randomization) was not used.[11] The current labeling for ceftaroline describes adverse reactions by pooling four Phase 3 clinical trials (2 in ABSSSI and 2 in CABP).[1]

***Reviewer comment**: Given the advantages and disadvantages of the different approaches of grouping pediatric studies for the safety analyses, the Division agreed to allow the Sponsor to submit an analysis of adverse reactions by treatment arm with all three pediatric randomized trials pooled together, as proposed at the pre-NDA meeting. In addition, the Sponsor was requested to carry out safety analyses by treatment arm for the individual indications [ABSSSI and CABP (naïve pooling MRSA and uncomplicated)].*

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Sponsor submits data from 3 active control studies and 2 single dose PK studies where a total of 319 pediatric subjects were treated with ceftaroline fosamil (**Table 12**).

Table 12 Safety Population, Size and Denominators

Study	Ceftaroline fosamil (n)	Comparator (n)
Active Control[1]		
P903-23 (ABSSSI)	106	53
P903-31 (CABP)	121	39
P903-24 (complicated CABP)	30	10
Total multiple dose	257	102
Single-dose PK		
P903-21	53	-
P903-15	9	-
Total single dose	62	
Total exposure	319	102

[1]Number of subjects in safety population used.

The duration of exposure to the study drug (IV and oral) was similar between the ceftaroline and comparator groups, and between subjects with CABP and ABSSSI, for the three active-controlled studies (**Table 13**).

Table 13 Extent of Exposure Across the Completed Active-controlled Studies in Pediatric Subjects—Safety Population

Parameter	*ABSSSI Study P903-23*		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106)	*Comparators (N = 53)*	*Ceftaroline (N = 151)*	*Comparators (N = 49)*	*Ceftaroline (N = 257)*	*Comparators (N = 102)*
Calendar days on all study drug (IV or oral)						
Mean (SD)	9.8 (3.5)	8.9 (3.5)	10.7 (4.0)	11.2 (3.3)	10.3 (3.8)	10.0 (3.6)
Median (min, max)	10.0 (2, 23)	10.0 (1, 15)	10.0 (1, 22)	11.0 (5, 20)	10.0 (1, 23)	10.0 (1, 20)
< 3 days, n (%)[a]	2 (1.9)	2 (3.8)	2 (1.3)	0	4 (1.6)	2 (2.0)
3 to 5 days, n (%)	11 (10.4)	8 (15.1)	8 (5.3)	1 (2.0)	19 (7.4)	9 (8.8)
6 to 8 days, n (%)	26 (24.5)	15 (28.3)	37 (24.5)	9 (18.4)	63 (24.5)	24 (23.5)
9 to 15 days, n (%)	63 (59.4)	28 (52.8)	92 (60.9)	34 (69.4)	155 (60.3)	62 (60.8)
16 to 22 days, n (%)	3 (2.8)	0	12 (7.9)	5 (10.2)	15 (5.8)	5 (4.9)
> 22 days, n (%)	1 (0.9)	0	0	0	1 (0.4)	0
Calendar days on IV study drug						
Mean (SD)	5.8 (2.5)	5.6 (2.5)	6.7 (3.0)	7.3 (2.6)	6.4 (2.9)	6.4 (2.7)
Median (min, max)	5.0 (2, 14)	5.0 (1, 14)	6.0 (1, 19)	7.0 (4, 13)	6.0 (1, 19)	6.0 (1, 14)
< 3 days, n (%)[a]	4 (3.8)	2 (3.8)	3 (2.0)	0	7 (2.7)	2 (2.0)
3 to 5 days, n (%)	54 (50.9)	28 (52.8)	64 (42.4)	16 (32.7)	118 (45.9)	44 (43.1)
6 to 8 days, n (%)	33 (31.1)	17 (32.1)	48 (31.8)	20 (40.8)	81 (31.5)	37 (36.3)
9 to 15 days, n (%)	15 (14.2)	6 (11.3)	35 (23.2)	13 (26.5)	50 (19.5)	19 (18.6)
16 to 22 days, n (%)	0	0	1 (0.7)	0	1 (0.4)	0
> 22 days, n (%)	0	0	0	0	0	0
Total doses of ceftaroline						
Mean (SD)	14.7 (7.4)	—	17.5 (9.2)	—	16.3 (8.6)	—
Median (min, max)	12.0 (3, 41)	—	15.0 (2, 54)	—	15.0 (2, 54)	—
Switched to oral study drug? n (%)						
Yes, N1	65 (61.3)	28 (52.8)	101 (66.9)	35 (71.4)	166 (64.6)	63 (61.8)
No	41 (38.7)	25 (47.2)	50 (33.1)	14 (28.6)	91 (35.4)	39 (38.2)

Parameter	*ABSSSI Study P903-23*		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106)	*Comparators (N = 53)*	*Ceftaroline (N = 151)*	*Comparators (N = 49)*	*Ceftaroline (N = 257)*	*Comparators (N = 102)*
Oral study drug received n/N1 (%)[b]						
Amoxicillin clavulanate	—	—	87 (86.1)	31 (88.6)	87 (52.4)	31 (49.2)
Cephalexin	41 (63.1)	17 (60.7)	—	—	41 (24.7)	17 (27.0)
Clindamycin	21 (32.3)	8 (28.6)	13 (12.9)	4 (11.4)	34 (20.5)	12 (19.0)
Linezolid	7 (10.8)	3 (10.7)	2 (2.0)	0	9 (5.4)	3 (4.8)
Study day of switch to oral study drug						
Mean (SD)	5.2 (2.1)	4.8 (1.4)	6.1 (2.7)	6.8 (2.3)	5.7 (2.5)	5.9 (2.2)
Median (min, max)	4.0 (2, 13)	4.0 (3, 9)	5.0 (2, 19)	6.0 (4, 13)	5.0 (2, 19)	5.0 (3, 13)
Calendar days on oral study drug						
Mean (SD)	7.3 (2.8)	7.3 (2.4)	6.8 (2.8)	6.4 (2.0)	7.0 (2.8)	6.8 (2.2)
Median (min, max)	8.0 (3, 17)	8.0 (2, 11)	7.0 (2, 20)	6.0 (3, 10)	7.0 (2, 20)	7.0 (2, 11)

a Percentages are calculated as 100 × (n/N).
b Percentages are calculated as 100 × n/N1.
Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; IV = intravenous; max = maximum; min = minimum; N = number of subjects in the Safety Population; n = number of subjects within a specific category; N1 = number of subjects who have taken IV and then switched to oral therapy; SD = standard deviation.
Source: Appendix Table 2.1.1.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety, Table 4.2.1-1.

All 62 subjects in the PK studies received a single dose of ceftaroline fosamil.

In the four pooled Phase 3 studies in adult subjects with cSSSI or CABP, 1300 subjects received ceftaroline fosamil and 1297 subjects received comparators in the safety population (NDA 200327 Clinical Review, Table 64).

***Reviewer comment**: It should be noted that the Sponsor is seeking approval in all pediatric age groups from 2 months to < 18 years. The number of pediatric patients in each age cohort is relatively small and may pose a challenge to identify age group specific safety signals*

8.2.2. Baseline demographic and other characteristics

Baseline demographic and other characteristics for the Group 1 studies are summarized in **Table 14**.

Table 14 Demographic and Other Baseline Characteristics Across the Completed Active-controlled Studies in Pediatric Subjects—Safety Population.

Parameter	*ABSSSI Study P903-23*		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106)	*Comparators (N = 53)*	*Ceftaroline (N = 151)*	*Comparators (N = 49)*	*Ceftaroline (N = 257)*	*Comparators (N = 102)*
Age (years)						
Mean (SD)	7.04 (5.10)	6.84 (5.25)	4.75 (3.80)	4.56 (3.92)	5.70 (4.51)	5.75 (4.78)
Median (min, max)	7.0 (0.2, 17.0)	6.0 (0.6, 17.0)	4.0 (0.2, 17.0)	3.0 (0.3, 16.0)	5.0 (0.2, 17.0)	4.0 (0.3, 17.0)
Age cohort, n (%)						
12 years to < 18 years	23 (21.7)	13 (24.5)	13 (8.6)	4 (8.2)	36 (14.0)	17 (16.7)
6 years to < 12 years	36 (34.0)	15 (28.3)	33 (21.9)	11 (22.4)	69 (26.8)	26 (25.5)
24 months to < 6 years	23 (21.7)	12 (22.6)	76 (50.3)	25 (51.0)	99 (38.5)	37 (36.3)
2 months to < 24 months	24 (22.6)	13 (24.5)	29 (19.2)	9 (18.4)	53 (20.6)	22 (21.6)
Sex, n (%)						
Male	56 (52.8)	32 (60.4)	85 (56.3)	26 (53.1)	141 (54.9)	58 (56.9)
Female	50 (47.2)	21 (39.6)	66 (43.7)	23 (46.9)	116 (45.1)	44 (43.1)
Race, n (%)						
White	90 (84.9)	49 (92.5)	146 (96.7)	46 (93.9)	236 (91.8)	95 (93.1)
Black or African American	15 (14.2)	4 (7.5)	2 (1.3)	1 (2.0)	17 (6.6)	5 (4.9)
Asian	0	0	2 (1.3)	1 (2.0)	2 (0.8)	1 (1.0)
Other	1 (0.9)	0	1 (0.7)	1 (2.0)	2 (0.8)	1 (1.0)
Weight (kg)						
Mean (SD)	30.2 (21.1)	30.6 (21.5)	21.8 (16.0)	21.0 (16.1)	25.3 (18.7)	26.0 (19.6)
Height (cm)						
Mean (SD)	120 (35.0)	122 (36.4)	109 (27.0)	107 (26.1)	113 (31.0)	115 (32.6)

Parameter	*ABSSSI Study P903-23*		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106)	*Comparators (N = 53)*	*Ceftaroline (N = 151)*	*Comparators (N = 49)*	*Ceftaroline (N = 257)*	*Comparators (N = 102)*
BMI (kg/m^2)						
Mean (SD)	18.3 (4.0)	18.0 (3.5)	16.7 (3.5)	16.4 (3.7)	17.3 (3.7)	17.2 (3.7)
Creatinine clearance ($mL/min/1.73\ m^2$)						
Mean (SD)	119 (33.7)	119 (36.3)	107 (31.3)	112 (51.9)	112 (32.8)	116 (44.5)
Creatinine clearance category, n (%)						
≥ 80 ($mL/min/1.73\ m^2$)	98 (92.5)	46 (86.8)	120 (79.5)	35 (71.4)	218 (84.5)	81 (79.4)
≥ 50 to < 80 ($mL/min/1.73\ m^2$)	6 (5.7)	6 (11.3)	30 (19.9)	14 (28.6)	36 (14.0)	20 (19.6)
< 50 ($mL/min/1.73\ m^2$)	1 (0.9)	0	0	0	1 (0.4)	0

Percentages are calculated as 100 × (n/N).
Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; BMI = body mass index; CABP = community-acquired bacterial pneumonia; max = maximum; min = minimum; N = number of subjects in the Safety Population; n = number of subjects within a specific category.
Source: Appendix Table 1.1.1.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety, Table 4.3.1.1-1.

Baseline demographic and other baseline characteristics for the pediatric pharmacokinetic studies are described in **Table 15** and **Table 16**.

In Study P903-21, age cohorts were categorized as follows:

Cohort 1: ≥ 6 years to < 12 years;
Cohort 2: ≥ 24 months to < 6 years;
Cohort 3: 28 days to < 24 months;
Cohort 4: term (gestational age ≥ 38 weeks) neonates < 28 days;
Cohort 5: preterm (gestational age 32 - 37 weeks) neonates < 28 days

Study P903-15 enrolled subjects 12 to 17 years of age.

Similar to the active control studies, more males than females were enrolled in both PK studies.

Table 15 Demographic Characteristics for Pharmacokinetic Studies—Safety Population (P903-21 pooled and P903-15).

Characteristic	*Study P903-15* *Total* *N = 9*	*Study P903-21* *Total* *N = 53*
Age, years[a]		
Mean (SD)	13.7 (1.8)	6.2 (3.1)[b]
Median (min, max)	13.0 (12, 16)	(2, 11)[c]
Age, days		
12 months to < 24 months, (mean [min, max])	NA	574 (426, 698)
28 days to < 12 months, (mean [min, max])	NA	168.5 (72, 337)
Term neonates > 14 days to < 28 days, (mean [min, max])	NA	19.7 (18, 22)
Term neonates 0 to 14 days, (mean [min, max])	NA	4.5 (0, 11)
Preterm neonates > 14 days to < 28 days, (mean [min, max])	NA	23.2 (15, 27)
Preterm neonates 0 to 14 days, (mean [min, max])	NA	4.5 (1, 9)
Sex, n (%)		
Male	5 (55.6)	34 (64.2)
Female	4 (44.4)	19 (35.8)
Race, n (%)		
White	6.(66.7)	29 (54.7)
Black or African American	2 (22.2)	21 (39.6)
American Indian or Alaska Native	0	1 (1.9)
Other	1 (11.1)	2 (3.8)
Weight, kg		
Mean (SD)	55.9 (12.8)	13.5 (15.1)
12 months to < 24 months, (mean [min, max])	NA	10.3 (8.5, 11.7)
28 days to < 12 months, (mean [min, max])	NA	8.0 (5.3, 12.5)
Term neonates > 14 days to < 28 days, (mean [min, max])	NA	4.1 (3.8, 4.6)
Term neonates 0 to 14 days, (mean [min, max])	NA	3.6 (3.0, 4.1)
Preterm neonates > 14 days to < 28 days, (mean [min, max])	NA	3.2 (2.6, 4.1)
Preterm neonates 0 to 14 days, (mean [min, max])	NA	2.1 (1.5, 3.3)
BMI, kg/m^2		
Mean (SD)	21.5 (3.1)	16.0 (4.9)
12 months to < 24 months, (mean [min, max])	NA	17.0 (14.3, 21.4)
28 days to < 12 months, (mean [min, max])	NA	19.1 (15.8, 22.8)
Term neonates > 14 days to < 28 days, (mean [min, max])	NA	14.2 (13.4, 15.7)
Term neonates 0 to 14 days, (mean [min, max])	NA	13.5 (11.4, 15.2)
Preterm neonates > 14 days to < 28 days, (mean [min, max])	NA	12.1 (10.0, 14.3)
Preterm neonates 0 to 14 days, (mean [min, max])	NA	9.5 (8.5, 10.8)
CrCl, mL/minute		
Mean (SD)	157 (63.5)[a]	138 (47.5)

a Age at time of first visit.
b Age in years was derived for subjects in Cohorts 1 (≥ 6 years to < 12 years) and 2 (≥ 24 months to < 6 years) only (n = 18).
c Minimum and maximum only.
d Units are $mL/min/1.73\ m^2$.
Abbreviations: BMI = body mass index; CrCl = creatinine clearance; CSR = clinical study report; min = minimum; max = maximum; n = number of subjects within a specific category; NA = not applicable.
Source: CSR P903-15, Table 10.3-1, CSR P903-21, Table 10.1.2-1 and Table 10.1.2-2.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety, Table 4.3.2-1.

Table 16 Summary of Demographic and Baseline Characteristics by Cohort —Safety Population (P903-21)

Demographic Variable		*Cohort 1 (N = 10)*	*Cohort 2 (N = 8)*	*Cohort 3 (N = 12)*	*Cohort 4 (N = 12)*	*Cohort 5 (N = 11)*	*Overall (N = 53)*
Race, n (%)	White	5 (50.0)	4 (50.0)	7 (58.3)	5 (41.7)	8 (72.7)	29 (54.7)
	Black or African American	4 (40.0)	4 (50.0)	4 (33.3)	6 (50.0)	3 (27.3)	21 (39.6)
	American Indian or Alaska Native	0	0	1 (8.3)	0	0	1 (1.9)
	Other	1 (10.0)	0	0	1 (8.3)	0	2 (3.8)
Sex, n (%)	Male	5 (50.0)	4 (50.0)	10 (83.3)	6 (50.0)	9 (81.8)	34 (64.2)
	Female	5 (50.0)	4 (50.0)	2 (16.7)	6 (50.0)	2 (18.2)	19 (35.8)
Ethnicity, n (%)	Non-Hispanic	10 (100)	7 (87.5)	11 (91.7)	11 (91.7)	9 (81.8)	48 (90.6)
	Hispanic	0	1 (12.5)	1 (8.3)	1 (8.3)	2 (18.2)	5 (9.4)
Mean age, years[a]		8.4	3.4	-	-	-	6.2
SD (range)		2.0 (6, 11)	1.3 (2, 5)	-	-	-	3.1 (2, 11)

Demographic Variable	*Cohort 1 (N = 10)*	*Cohort 2 (N = 8)*	*Cohort 3 (N = 12)*	*Cohort 4 (N = 12)*	*Cohort 5 (N = 11)*	*Overall (N = 53)*
Mean age, days[b]	-	-	371.3	12.1	13.0	135.5
SD (range)	-	-	232.5 (72, 698)	8.5 (0, 22)	10.6 (1, 27)	217.7 (0, 698)
Mean gestational age, weeks[c]	-	-	37.8	39.2	35.2	37.4
SD (range)	-	-	4.2 (25, 40)	0.7 (38, 40)	1.8 (32, 37)	3.1 (25, 40)
Mean weight, kg	37.78	19.08	9.15	3.85	2.59	13.49
SD (range)	18.10 (18.9, 74.9)	3.21 (13.6, 22.7)	2.28 (5.3, 12.5)	0.47 (3.0, 4.6)	0.84 (1.5, 4.1)	15.12 (1.5, 74.9)
Mean height, cm	131.17	104.74	71.04	52.65	48.63	78.66
SD (range)	14.91 (110.0, 152.0)	7.66 (94.0, 114.5)	9.38 (54.0, 85.0)	1.75 (49.5, 55.0)	5.50 (42.0, 58.4)	32.66 (42.0, 152.0)
Mean BMI, kg/m^2	20.95	17.35	18.06	13.86	10.70	16.02
SD (range)	6.62 (15.3, 32.4)	2.13 (13.9, 20.7)	2.79 (14.3, 22.8)	1.29 (11.4, 15.7)	1.86 (8.5, 14.3)	4.88 (8.5, 32.4)
Mean CrCl[d], $mL/min/1.73\ m^2$	169.62	127.28	119.35	-	-	138.22
SD (range)	53.50 (104.5, 249.5)	40.45 (78.2, 204.5)	34.69 (67.5, 185.0)	-	-	47.54 (67.5, 249.5)
Mean Urine output[e], mL/kg/hr	-	-	3.20	5.39	4.90	5.06
SD (range)	-	-	- (3.2, 3.2)	2.98 (1.9, 10.3)	1.89 (2.7, 8.4)	2.42 (1.9, 10.3)

Notes: Cohort 1: ≥ 6 years to < 12 years; Cohort 2: ≥ 24 months to < 6 years; Cohort 3: 28 days to < 24 months; Cohort 4: term (gestational age ≥ 38 weeks) neonates < 28 days; Cohort 5: preterm (gestational age 32 - 37 weeks) neonates < 28 days.

Abbreviations: BMI = body mass index; CrCl = creatinine clearance; hr = hour; min = minutes; N = number of subjects in Safety Population; n = number of subjects in specific category.

a Age in years was derived for subjects in Cohorts 1 and 2 only (n = 18).

b Age in days was derived for subjects in Cohorts 3, 4, and 5 only (n = 35).

c Gestational age was collected for subjects in Cohorts 3, 4, and 5 only (n = 35).

d CrCl was estimated for subjects in Cohorts 1, 2, and 3 (> 3 months of age only) (n = 30); CrCl was derived differently for subjects enrolled under the Original Protocol and Protocol Amendment 1 than for subjects enrolled under later amendments because a different Schwartz formula was introduced in Protocol Amendment 2 (Section 9.7.1.3.1).

e Urine output was collected for subjects in Cohorts 3 (≤ 3 months of age only), 4, and 5 (n = 23).

Source: Table 14.3.2.1.1.

Source: NDA 200327 Study P903-21 Clinical Study Report, Table 10.1.2-1.

8.2.3. Adequacy of the safety database:

The Sponsor submits pediatric safety data for 319 individual subjects (257 multiple-dose exposure and 62 single dose exposure). The data is distributed similarly in all age cohorts. The pediatric safety database is adequate for review. However, the number of children in each cohort is relatively small for subset analyses.

***Reviewer comment**: In addition to data for ceftaroline fosamil submitted by the Sponsor, there are extensive safety data available from the use of the cephalosporin class of antibiotics in all age groups, including neonates, infants and young children.*

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There are two issues regarding data integrity and submission quality worth noting.

First, in Study P903-23, there is one subject randomized to the ceftaroline fosamil group who received treatment with cefazolin. Data for this subject are included in the randomized treatment group for efficacy analyses (N = 107 for ceftaroline fosamil group; N = 52 for comparator group) and are included by treatment received for safety analyses (N = 106 for ceftaroline fosamil group; N = 53 for comparator group).

Second, there are two sites (Site Number 702 and 804) from study P903-23 where financial disclosures were not obtained from Principal Investigators and Sub-Investigators by the Sponsor. These sites enrolled 7 subjects total, all in the ceftaroline arm. Because subjects from sites 702 (n=6) and 804 (n=1) were exposed to ceftaroline fosamil and add data to the pediatric safety database, all 7 subjects were included in the safety analyses.

8.3.2. Categorization of Adverse Events

In the Group 1 studies, an AE occurring after the start of the first dose of study drug and up until 30 days after the last dose of study drug was considered a TEAE if it was not present before the start of the first dose of study drug, or it was present before the start of the first dose of study drug but increased in severity after the start of the first dose of study drug. If more than 1 AE with the same preferred term (PT) was reported before the start of the first dose of study drug, the AE with the greatest severity was used for comparison with the AEs occurring after the start of the first dose of study drug. A spontaneously reported AE after the late-follow-up (LFU) visit, or after 30 days after last dose of study drug (if the LFU visit was not performed or was performed less than 30 days after the last dose of study drug), was not counted as a TEAE. Version 17.0 of the *Medical Dictionary for Regulatory Activities* (MedDRA)

was used for coding AEs across all individual studies in Group 1.

AEs from the Group 2 studies are presented as they appear in the respective CSRs. For Study P903-15, adverse events were coded using version 11.1 of MedDRA. For Study P903-21, adverse events were coded using version 15.1 of MedDRA.

8.3.3. Routine Clinical Tests

Please refer to the schedule of assessments and procedures for each individual study discussed in **Section 6**.

8.3.4. Deaths

There were no deaths in the Group 1 pediatric active controlled studies or the Group 2 pediatric PK studies.

In the pooled Phase 3 cSSSI and CABP studies in adult subjects, the number of deaths reported before the LFU visit was similar in the ceftaroline and comparator groups (18 [1.4%] vs 12 [0.9%], respectively). Cardiac, respiratory, neoplastic, and infectious etiologies accounted for the deaths.

8.3.5. Serious Adverse Events

Serious adverse events were reviewed for the Group1 and Group 2 studies.

GROUP 1 STUDIES

In the pooled Group 1 studies, the incidence of serious adverse events was similar for ceftaroline and comparator (10 out of 257 [3.9%] vs. 3 out of 102 [2.9%], respectively) (**Table 17**). SAEs in the ceftaroline fosamil arm included pneumonia viral, clostridium difficile colitis, hypersensitivity, osteomyelitis, pneumonia respiratory syncytial virus, infectious pleural effusion, dehydration, gastroenteritis, bronchitis, pneumonia, SAEs in the comparator arm included lymphadenitis, tonsillitis, pulmonary thrombosis, viral upper respiratory tract infection and lower respiratory tract infection viral.

Table 17 Incidence of Serious Adverse Events by System Organ Class and Preferred Term Across the Completed Active-controlled Studies in Pediatric Subjects—Safety Population.

System Organ Class *Preferred Term*	*ABSSSI Study P903-23*		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106) n (%)	*Comparators (N = 53) n (%)*	*Ceftaroline (N = 151) n (%)*	*Comparators (N = 49) n (%)*	*Ceftaroline (N = 257) n (%)*	*Comparators (N = 102) n (%)*
Subjects with at least 1 SAE	*4 (3.8)*	*1 (1.9)*	*6 (4.0)*	*2 (4.1)*	*10 (3.9)*	**3 (2.9)**
Blood and lymphatic system disorders						
Lymphadenitis	0	1 (1.9)	0	0	0	1 (1.0)
Immune system disorders						
Hypersensitivity	1 (0.9)	0	0	0	1 (0.4)	0
Infections and infestations						
Gastroenteritis	0	0	2 (1.3)	0	2 (0.8)	0
Bronchitis	0	0	1 (0.7)	0	1 (0.4)	0
Clostridium difficile colitis	1 (0.9)	0	0	0	1 (0.4)	0
Infectious pleural effusion	0	0	1 (0.7)	0	1 (0.4)	0
Osteomyelitis	1 (0.9)	0	0	0	1 (0.4)	0
Pneumonia	0	0	1 (0.7)	0	1 (0.4)	0
Pneumonia respiratory syncytial viral	0	0	1 (0.7)	0	1 (0.4)	0
Pneumonia viral	1 (0.9)	0	0	0	1 (0.4)	0
Lower respiratory tract infection viral	0	0	0	1 (2.0)	0	1 (1.0)
Tonsillitis	0	1 (1.9)	0	0	0	1 (1.0)
Viral upper respiratory tract infection	0	0	0	1 (2.0)	0	1 (1.0)
Metabolism and nutrition disorders						
Dehydration	0	0	1 (0.7)	0	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders						
Pulmonary thrombosis	0	0	0	1 (2.0)	0	1 (1.0)

Percentages are calculated as 100 × (n/N).
Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; N = number of subjects in the Safety Population; n = number of subjects within a specific category; SAE = serious adverse event.
Source: Appendix Table 3.4.1.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety, Table 5.1.4.1-1.

CRFs and the Applicant's narrative summaries were used to review details of serious adverse events. A tabular summary of nonfatal serious adverse events in the Group 1 studies are included in **Appendix 13.10** for reference. Additional details can be found in the relative clinical study report or case report form.

GROUP 2 STUDIES

In the Group 2 studies, there were 4 subjects experiencing an SAE. Dictionary derived terms for the SAEs included 'anaemia neonatal', 'rash', 'tremor', and 'pathologic fracture'.

A tabular summary of nonfatal serious adverse events in the Group 2 studies are included in **Appendix 13.11** for reference. Additional details can be found in the relative clinical study report or case report form.

Comparison with Adult Phase 3 Studies

In the pooled Phase 3 adult studies, SAEs were reported in 99 subjects (7.6%) in the ceftaroline group and in 100 subjects (7.7%) in the comparator group. In the Group 1 pediatric studies, there was a lower percentage of SAEs reported compared to the adult studies for both treatment arms (3.9%, ceftaroline; 2.9% comparator).

In the pooled Phase 3 adult studies, the most common SAEs in the ceftaroline group were pneumonia, pulmonary embolism, and pleural effusion. The most common SAEs in the comparator group were pneumonia, chronic obstructive pulmonary disease, and pleural effusion.

Reviewer comment*: The nature of SAEs in the pediatric studies was different than the adult studies, encompassing a variety of infectious etiologies. There were two subjects from the Group 1 pediatric studies who appeared to experience an SAE related to ceftaroline. These SAEs were clostridium difficile colitis and hypersensitivity, both known to be associated with ceftaroline as well as any other cephalosporin. In addition, clostridium difficile colitis and hypersensitivity are listed in the Warnings and Precautions section of the current label for ceftaroline fosamil.*[1] *The age range of the subjects experiencing SAEs was wide. Small sample size precludes determination of an association of SAEs with a particular age cohort or race.*

8.3.6. Dropouts and/or Discontinuations Due to Adverse Effects

GROUP 1 STUDIES

In the pooled Group 1 studies, 10 subjects (3.9%) in the ceftaroline group experienced at least 1 AE leading to discontinuation of study drug compared with 2 subjects (2.0%) in the comparator group. The majority of TEAEs leading to study drug discontinuation were in Skin and Subcutaneous Tissue Disorders SOC (4/10 [40%]) (**Appendix 13.13**, **)**. Preferred terms included rash, rash macular, urticaria, and pruritus. All events except rash (n = 2) were reported in 1 subject each. A line listing for subjects experiencing an adverse event leading to discontinuation of study drug is presented in **Appendix 13.14**.

GROUP 2 STUDIES

Study P903-21

No subjects discontinued treatment due to adverse events in study P903-21.

Study P903-15

In study P903-15, there was one subject who prematurely discontinued from study drug after receiving about 80% of the total dose (199 mL of 250 mL) because of a TEAE, extravasation at the infusion site. The subject completed the study.

COMPARISON WITH ADULT PHASE 3 STUDIES

In the adult Phase 3 studies, 34 subjects (2.6%) in the ceftaroline group and 46 subjects (3.5%) in the comparator group, prematurely discontinued study drug because of TEAEs. This is similar to findings from the pediatric Group 1 studies (ceftaroline, 10 subjects [3.9%]); comparator 2 subjects [2.0%]).

Reviewer Comment: *The frequency of dropouts and discontinuations, as well as study drug discontinuations due to a TEAE, in the pediatric Group 1 and Group 2 studies is acceptable. The majority of TEAEs leading to study drug discontinuation were in Skin and Subcutaneous Tissue Disorders SOC (4/10 [40%]). Preferred terms included rash, rash macular, urticaria, and pruritus. All of the aforementioned terms are indicative of a hypersensitivity reaction and are known to occur with ceftaroline treatment. In the four adult pooled Phase 3 studies, treatment discontinuation due to adverse reactions occurred in 35/1300 (2.7%) of patients receiving Teflaro and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse reactions leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the Teflaro group and 0.5% in comparator group.[1] Furthermore, 'Hypersensitivity Reactions' is listed in the Warnings and Precautions section of the ceftaroline label. No pattern in TEAEs leading to discontinuation of study drug was observed with respect to sex or race; however small sample sizes preclude making definitive conclusions.*

8.3.7. Significant Adverse Events

The following treatment emergent adverse events of interest were evaluated in the Group 1 studies, based on the Warnings and Precautions section of the current ceftaroline fosamil label[1], postmarketing safety concerns, and other common areas of clinical concern (**Table 18**). Each TEAE of significance is described in the relevant section. Standard MedDRA Queries (SMQ) were conducted using MedDRA version 17.0.

Table 18 Analytical Approach for Evaluating Significant Adverse Events.

	Significant Adverse Event	Analytical Approach*
A	**Warnings and Precautions Section of Label**	
1	Hypersensitivity Reactions	Narrow SMQ search 'Hypersensitivity'
2	Clostridium difficile Associated Diarrhea	Broad SMQ search 'pseudomembranous colitis'
3	Direct Coombs' Test Seroconversion/ Hemolytic Anemia	Shifts from baseline Direct Coombs' Test Broad SMQ search 'Haematopoietic erythropenia' Query of selected preferred terms associated with hemolytic anemia
4	Development of Drug-Resistant Bacteria	Query of selected preferred terms associated with development of drug-resistant bacteria
B	**Postmarketing Safety Concerns**	
5	Bone marrow suppression (Agranulocytosis, leukopenia, neutropenia)	Broad SMQ search 'Haematopoietic cytopenias' Narrow SMQ search 'Agranulocytosis'
6	Eosinophlic pneumonia	Narrow SMQ search 'Eosinophilic pneumonia'
C	**Common areas of clinical concern**	
7	Convulsions/ Seizures	Broad SMQ search 'convulsions'
8	Renal Impairment	Broad SMQ search 'acute renal failure' associated with renal impairment
9	Drug-induced Liver Injury	Narrow SMQ search 'Drug related hepatic disorders – comprehensive search'

**Safety population used.*

A. Warnings and Precautions Section of Label

1. Hypersensitivity Reactions

A narrow SMQ search of 'Hypersensitivity' was conducted on the safety population of the Group 1 studies. The percentage of subjects with TEAEs of hypersensitivity was similar in the 2 treatment groups (ceftaroline: n = 28 [10.9%]; comparators: n = 12 [11.8%]) **Appendix 13.15**. Most of these TEAEs were rash-related in the Skin and Subcutaneous Disorders SOC.

There was one subject (**P903-23.021923002**) in the ceftaroline group who had an SAE of 'hypersensitivity'. Please see details in **Section 8.3.5 Serious Adverse Events**.

In addition, the following TEAEs were associated with study drug discontinuation in the ceftaroline fosamil group: Rash, Rash macular, Urticaria, and Pruritus. Please see details in **Section 8.3.6 Dropouts and/or Discontinuations**. There were no subjects in the comparator group who discontinued study drug due to a TEAE in the Skin and Subcutaneous Disorders SOC.

In the pooled adult Phase 3 studies, the percentages of subjects with TEAEs associated with allergic reactions in the ceftaroline group was slightly higher than the comparator group (n = 70 [5.4%] vs n = 111 [8.5%], respectively). There were 5 subjects with SAEs representing potential allergic reactions with a similar incidence in both arms (ceftaroline, n=3; comparator n=2). The SAEs in the ceftaroline group included hypersensitivity, anaphylactoid reaction, and anaphylactic shock while the SAE of hypersensitivity occurred in both subjects in the comparator group. The percentage of subjects discontinuing from the study or study drug due to a possible allergic reaction was low and similar in both arms (ceftaroline, n=15 [1.1%] and comparator, n=23 [1.8%]).

Reviewer comment: *Hypersensitivity reactions are a known adverse reaction from cephalosporin use in general. The incidence of TEAEs associated with hypersensitivity is similar in the ceftaroline and comparator arms in the pediatric studies. In contrast, in the adult Phase 3 studies, the incidence of ceftaroline fosamil was slightly higher in the ceftaroline group versus the comparator group (n=111 [8.5%] versus n=70 [5.4%], respectively). 'Hypersensitivity' is listed in the Warnings and Precautions Section of the label. 'Hypersensitivity' is also listed as an adverse reaction observed during clinical trials in the Adverse Reactions section of the current ceftaroline fosamil label.*[1] *Based on the available data, labelling should be similar to adults and incorporate information from pediatric studies with regards to possible hypersensitivity reactions occurring at high frequency (i.e. all types of rashes).*

2. Clostridium difficile Associated Diarrhea

A broad search of the SMQ 'pseudomembranous colitis' revealed a similar percentage of patients with TEAEs in the SMQ in both the ceftaroline and comparator arms (8.2% versus 11.8%, respectively) (**Appendix 13.15**,).

Details regarding 1 subject (**P903-23.006323001**) with a SAE of severe *C. dificile* colitis are described in **Section 8.3.5**

Potential antibiotic-associated diarrhea reported in the active-controlled Phase 3 adult studies was similar in the ceftaroline and comparator arms (n = 59 [4.5%] versus n = 42 [3.2%], respectively). In the cSSSI studies, there were 2 subjects (0.2%) in the ceftaroline arm and 1 subject (<0.1%) in the comparator group with confirmed *C. difficile.* One of the 2 subjects in the ceftaroline fosamil arm had a TEAE of *C. difficile* colitis reported as an SAE.

Reviewer comment: *No additional labelling change for pediatrics is recommended based on the available data. Cephalosporin use in general is associated with C. difficile associated diarrhea. The incidence of potential antibiotic associated diarrhea associated with ceftaroline fosamil use*

in the pediatric population appears to be similar to the comparator, as well as the adult population. 'Clostridium difficile-associated diarrhea' is listed in the Warnings and Precautions Section of the label. 'Clostridium difficile colitis' is listed as an adverse reaction observed during clinical trials in the Adverse Reactions section of the current ceftaroline fosamil label.[1]

3. Direct Coombs' Test Seroconversion/ Hemolytic Anemia

Direct Coombs' Test Seroconversion

In all of the Group 1 studies, Direct Coombs' test seroconversions occurred in a higher percentage of pediatric subjects in the ceftaroline group than in the comparator groups (P903-23 [ceftaroline 17.2%; comparators 4.2%], P903-31 [ceftaroline: 17.0%; comparators 2.7%], and P903-24 [ceftaroline: 26.1%; comparators: 0%]).

Similarly, in the adult pooled phase 3 studies, the incidence of subjects with direct Coombs' test seroconversions was higher in the ceftaroline group compared with the comparator group (10.7% vs 4.4%, respectively).

Reviewer comment: *Direct Coombs' test seroconversion is a known adverse reaction associated with the use of ceftaroline fosamil and is listed in the Warnings and Precautions section of the current label. Similar to findings in the adult Phase 3 studies, the incidence of Direct Coombs' test seroconversion was higher in the ceftaroline arm versus the comparator arm in the pediatric studies. The pediatric subjects with Direct Coombs' test seroconversion did not have clinical evidence of hemolytic anemia or hemolysis. Based on review of the pediatric data, the fact that Direct Coombs' test seroconversion occurs in the pediatric population, in addition to the adult population, can be added to the Warnings and Precautions Section of the label.*

Hemolytic Anemia

In the Group 1 studies, a broad SMQ search of 'Haematopoietic erythropenia' revealed seven subjects with a TEAE of 'anemia' in the ceftaroline fosamil arm and one subject with a TEAE of 'anemia' in the comparator arm. There were no other TEAEs identified in either arm of the Group 1 studies noted in the broad SMQ search of 'Haematopoietic erythropenia'.

The Sponsor and the reviewer searched for the following preferred terms in the Group 1 studies:

> Autoimmune haemolytic anaemia, blood bilirubin increased, cold type haemolytic anaemia, coombs negative haemolytic anaemia, coombs positive haemolytic anaemia, evans syndrome, haematocrit decreased, haemoglobin decreased, haemolysis, haemolytic anaemia, haptoglobin decreased, intravascular haemolysis, isoimmune

haemolytic disease, microangiopathic haemolytic anaemia, red blood cell count decreased, reticulocyte count increased, reticulocyte percentage increased, reticulocytosis, and splenomegaly

Only one of the aforementioned preferred terms was found in either treatment arms. In the Group 1 studies, there was one subject (**P903-31.141331004**) with a TEAE of 'splenomegaly' in the ceftaroline treatment arm. There was no subject with a TEAE of 'splenomegaly' in the comparator arm.

In the Group 2 studies, there was one subject each with a TEAE of 'anemia neonatal' (**P903-21.01021004**) and 'anemia' (**P903-21.01521005**).

In the pooled Phase 3 adult studies, the incidence of TEAEs representing potential drug-induced anemia were similar in the ceftaroline and comparator groups (n = 16 [1.2%] vs n = 17 [1.3%], respectively).

Reviewer comment: *Drug-induced hemolytic anemia is described in the Warnings and Precautions section of the current ceftaroline fosamil label under the Direct Coombs' Test Seroconversion Section (5.3). 'Anemia' is an adverse event listed in the Section on Adverse Reactions Observed During Clinical Trials in the Adverse Reactions section of the current label. No additional labelling changes are recommended based on review of the pediatric data.*

4. Development of Drug-Resistant Bacteria

In the Group 1 studies, the Sponsor and this reviewer searched for the following preferred terms with respect to the development of drug-resistant bacteria:

Drug resistance, drug ineffective, drug tolerance, drug tolerance increased, no therapeutic response, pathogen resistance, tachyphylaxis, therapeutic product ineffective, therapeutic response decreased, treatment failure, drug effect decreased, antibiotic resistant staphylococcus test, antibiotic resistance staphylococcus test positive

There were no subjects in the ceftaroline fosamil or the comparator arm with any of the afore-mentioned TEAEs.

Reviewer comment: *No additional labelling recommendations are required based on the pediatric data. Development of drug-resistant bacteria is a known effect of exposure to cephalosporin class antibiotics. In addition, Development of Drug-Resistant Bacteria is listed in the Warnings and Precautions Section of the current ceftaroline fosamil label.*

B. Postmarketing safety concerns

5. Bone marrow suppression (Agranulocytosis, leukopenia, neutropenia)

In the Group 1 studies, a broad search of the SMQ 'haematopoietic cytopenias' revealed one subject from study P903-23 with a TEAE of 'neutropenia' in the ceftaroline fosamil arm and 0 subjects with neutropenia in the comparator arm. There were 7 (2.7%) subjects with a TEAE of 'anemia' in the ceftaroline fosamil arm and 1 (1.0%) subject in the comparator arm. No other TEAEs associated with the SMQ 'haematopoietic cytopenias' were identified in either arm.

A narrow SMQ search of 'Agranulocytosis' revealed no subjects in the Group 1 studies with an associated TEAE in either the ceftaroline fosamil or comparator arms.

In the Group 1 studies, there was one subject (**P903-23.002323002**) from P903-23 with a TEAE of 'neutropenia'. The subject was a 9 month White Hispanic male who developed neutropenia on study day 3. Neutropenia did not result in study drug discontinuation and resolved on study day 7.

In the Group 2 studies, there was one subject (**P903-21.01721003**) with a TEAE of 'neutrophil count decreased'.

Reviewer comment: *Administration of cephalosporins, including ceftaroline fosamil, especially at higher doses and longer durations than approved in labeling, is known to cause bone marrow suppression in some patients.*

The incidence of TEAEs associated with the broad SMQ search of 'haematopoietic cytopenias' was low and similar in both arms of the Group 1 pediatric studies.

'Neutropenia' is listed as an adverse reaction observed during clinical trials in the Adverse Reactions section of the current ceftaroline fosamil label.[1]

'Agranulocytosis' is listed in the postmarketing experience section of the Adverse Reactions section of the current label.[1]

It should be noted that 'Leukopenia' has been reported in post-marketing, however this adverse event is not included in the current label. Please see ***Section 8.8.1 Safety Concerns Identified Through Postmarket Experience*** *for additional details regarding the need to add 'leukopenia' as an adverse event observed in postmarketing in the label.*

6. Eosinophilic pneumonia

In the Group 1 studies, a narrow search of the SMQ 'eosinophilic pneumonia' revealed no subjects from either treatment arm with an associated TEAE.

However, a broad search of the SMQ 'eosinophilic pneumonia' revealed a slightly higher percentage of subjects with an associated TEAE occurring within the SMQ in the ceftaroline fosamil arm versus the comparator (n=14 [5.5%] versus n=2 [2%], respectively) (**Appendix 13.15,**).

In the Group 1 studies, there were no subjects who experienced a TEAE of eosinophilic pneumonia. In addition, there were no subjects who experienced a TEAE with the dictionary-derived terms of 'pneumonia' *and* 'eosinophilia', or 'pneumonia' *and* 'eosinophil count increased'. There was 1 subject each with a TEAE of 'eosinophil count increased' (**P903-31.141131002**) and 'eosinophilia' (**P903-24.002324005**) alone.

In the Group 2 studies, there were no subjects who experienced a TEAE of eosinophilic pneumonia, pneumonia, eosinophilia, or eosinophil count increased.

The Sponsor reports a post-marketing serious adverse event of 'eosinophilia' in a 17 year old male. In addition, there are published case reports of eosinophilic pneumonia associated with ceftaroline fosamil use in adults.

Reviewer comment: *'Eosinophilia' is listed as an adverse reaction observed during clinical trials in the Adverse Reactions section of the current ceftaroline fosamil label.[1] Specific cases of eosinophilic pneumonia were not identified in the safety review of the pediatric studies. The Office of Surveillance and Epidemiology is reviewing eosinophilic pneumonia associated with ceftaroline fosamil exposure reported through postmarketing. Please refer to* ***Section 8.8.1 Safety Concerns Identified Through Postmarket Experience*** *for additional details.*

C. Common areas of clinical concern

7. Convulsions/ Seizures

In the Group 1 studies, a broad search of the SMQ 'convulsions' revealed one subject from study P903-23 with a TEAE of 'febrile convulsion' in the ceftaroline fosamil arm. There were no subjects with a TEAE associated with the SMQ of 'convulsions' in the comparator arm in all of the Group 1 studies.

In the adult Phase 3 studies, 3 subjects experienced seizures: 1 in the ceftaroline group from a

cSSSI study and 2 (1 in the ceftaroline group and 1 in the comparator group) from CABP studies.

Reviewer comment: *Neurotoxicity, including convulsions, is a known adverse reaction of cephalosporins, particularly in patients with reduced renal function. Results in both the pediatric and adult active-controlled studies revealed a low and similar incidence of convulsions in the ceftaroline fosamil and comparator arms. 'Convulsion' is listed as an adverse reaction observed during clinical trials in the Adverse Reactions section of the current ceftaroline fosamil label.[1] The one case of 'febrile convulsion' identified in the pediatric study P903-23 may be related to underlying host factors rather than ceftaroline fosamil. No additional labelling change is recommended based on the available pediatric data.*

8. Renal Impairment

In a broad SMQ search of 'acute renal failure' in the Group 1 studies, there was one TEAE 'urine output decreased' with one subject (**P903-24.004324001**) in the ceftaroline fosamil arm and one subject (**P903-24.002124001**) in the comparator arm.

In the Group 1 studies, there was one subject (**P903-31.141531001**) with a TEAE of 'edema' in the ceftaroline treatment arm.

In the comparator arm of the Group 1 studies, there was one subject each with a TEAE of 'fluid retention' (**P903-31.141731011**), and 'edema peripheral' (**P903-24.002324003**).

In the Group 1 studies, the Sponsor and this reviewer searched for the following preferred terms with respect to renal impairment:

> Anuria, blood creatinine increased, cardiorenal syndrome, chronic allograft nephropathy, complications of transplanted kidney, creatinine renal clearance decreased, drug interaction, fluid retention, glomerular filtration rate decreased, haemolytic uremic syndrome, hepatorenal failure, hepatorenal syndrome, hypercreatininaemia, inhibitory drug interaction, kidney transplant rejection, nail-patella syndrome, oedema due to renal disease, oliguria, pancreatorenal syndrome, polyarteritis nodosa, postoperative renal failure, postrenal failure, potentiating drug interaction, renal and pancreas transplant rejection, renal failure acute, renal failure chronic, renal failure, renal impairment, scleroderma renal crisis, and tubulointerstitial nephritis

None of the aforementioned preferred terms were found in either treatment arm of the Group 1 studies.

Reviewer comment: *'Renal failure' is noted in the adverse reactions section of the current ceftaroline fosamil label. No additional labelling changes are recommended based on the review of the pediatric data.*

9. Drug-induced liver injury

A narrow SMQ search of 'Drug related hepatic disorders – comprehensive search' was conducted on the safety population of the Group 1 studies. The percentage of subjects with TEAEs of associated with this SMQ was similar in the 2 treatment groups (ceftaroline: n = 8 [3.1%]; comparators: n = 4 [3.9%]) (**Appendix 13.15,). One subject discontinued treatment with ceftaroline fosamil** because of severe ALT increased and severe AST increased. No subjects met criteria for Hy's law. Please see **Section 8.3.6 Dropouts and/or Discontinuations** for additional details.

In the pooled adult Phase 3 studies, the incidences of subjects in the ceftaroline and comparator groups with TEAEs representing possible liver injury were similar (n = 33 [2.5%] vs n = 47 [3.6%], respectively).

Reviewer comment: *Results in both the pediatric and adult active-controlled studies revealed a low and similar incidence of potential drug induced liver injury in the ceftaroline fosamil and comparator arms. 'Increased transaminases' and 'hepatitis' are listed as adverse reactions observed during clinical trials in the Adverse Reactions section of the current ceftaroline fosamil label.*[1] *Aside from reporting TEAEs occurring at 2% in the pediatric population (i.e. AST and ALT increased), no additional labelling change is recommended based on the available data.*

8.3.8. Treatment Emergent Adverse Events and Adverse Reactions

OVERVIEW

Across all three pooled active-controlled studies, the incidence of TEAEs was similar in the ceftaroline and comparator groups (45.9% versus 48.0%, respectively) (**Table 19**).

Table 19 Summary of Adverse Events Across the Completed Active-controlled, Parallel-group

	ABSSSI Study P903-23		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106) n (%)	*Comparators (N = 53) n (%)*	*Ceftaroline (N = 151) n (%)*	*Comparators (N = 49) n (%)*	*Ceftaroline (N = 257) n (%)*	*Comparators (N = 102) n (%)*
Number of subjects with:						
Any TEAE	51 (48.1)	23 (43.4)	67 (44.4)	26 (53.1)	118 (45.9)	49 (48.0)
Any treatment-related TEAE	23 (21.7)	12 (22.6)	19 (12.6)	6 (12.2)	42 (16.3)	18 (17.6)
Any SAE	4 (3.8)	1 (1.9)	6 (4.0)	2 (4.1)	10 (3.9)	3 (2.9)
AEs associated with discontinuation of study drug	4 (3.8)	2 (3.8)	6 (4.0)	0	10 (3.9)	2 (2.0)
Deaths	0	0	0	0	0	0

Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; AE = adverse event; CABP = community-acquired bacterial pneumonia; N = number of subjects in the Safety Population; n = number of subjects within a specific category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Module 2.7.4, Table 5.1-1.

Source: NDA 200327 Module 2.5 Clinical Overview, Table 5.3-1.

GROUP 1 STUDIES

In the Group 1 active-controlled studies, the incidence of TEAEs were similar between the ceftaroline and comparator groups (**Table 20**). TEAEs occurring in > 5% of subjects in the ceftaroline group included diarrhea (n = 20, 7.8%), vomiting (n = 13, 5.1%), and rash (n = 13, 5.1%). In the comparator group, TEAEs occurring in > 5% subjects included vomiting (n = 12, 11.8%) and diarrhea (n = 10, 9.8%). In subjects with TEAES occurring at ≥3% in each treatment group, 7 subjects (2.7%) in the ceftaroline group had at least 1 severe TEAE compared with 4 subjects (3.9%) in the comparator group.

Table 20 Incidence of Common (≥ 3%) Treatment-emergent Adverse Events by System Organ Class and Preferred Term Across the Completed Active-controlled, Parallel-group Clinical Studies in Pediatric Subjects—Safety Population

System Organ Class *Preferred Term*	*ABSSSI* *Study P903-23*		*CABP* *Studies P903-24 and P903-31*		*Pooled Studies* *P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106) *n (%)*	*Comparators (N = 53)* *n (%)*	*Ceftaroline (N = 151)* *n (%)*	*Comparators (N = 49)* *n (%)*	*Ceftaroline (N = 257)* *n (%)*	*Comparators (N = 102)* *n (%)*
Subjects with at least 1 TEAE	*51 (48.1)*	*23 (43.4)*	*67 (44.4)*	*26 (53.1)*	*118 (45.9)*	*49 (48.0)*
Blood and lymphatic system disorders						
Anaemia	0	0	6 (4.0)	1 (2.0)	6 (2.3)	1 (1.0)
Eosinophilia	5 (4.7)	1 (1.9)	1 (0.7)	0	6 (2.3)	1 (1.0)
Thrombocytosis	0	0	3 (2.0)	4 (8.2)	3 (1.2)	4 (3.9)
Gastrointestinal disorders						
Diarrhoea	8 (7.5)	8 (15.1)	12 (7.9)	2 (4.1)	20 (7.8)	10 (9.8)
Vomiting	7 (6.6)	8 (15.1)	6 (4.0)	4 (8.2)	13 (5.1)	12 (11.8)
Nausea	5 (4.7)	0	3 (2.0)	1 (2.0)	8 (3.1)	1 (1.0)
General disorders and administration site conditions						
Pyrexia	4 (3.8)	0	4 (2.6)	2 (4.1)	8 (3.1)	2 (2.0)
Infections and infestations						
Upper respiratory tract infection	5 (4.7)	1 (1.9)	1 (0.7)	2 (4.1)	6 (2.3)	3 (2.9)
Otitis media	0	0	1 (0.7)	3 (6.1)	1 (0.4)	3 (2.9)
Viral upper respiratory tract infection	0	0	1 (0.7)	2 (4.2)	1 (0.4)	2 (2.0)
Injury, poisoning and procedural complications						
Arthropod bite	0	2 (3.8)	0	0	0	2 (2.0)
Investigations						
Alanine aminotransferase increased	1 (0.9)	1 (1.9)	3 (2.0)	2 (4.1)	4 (1.6)	3 (2.9)
Metabolism and nutrition disorders						
Hypocalcaemia	0	0	1 (0.7)	2 (4.1)	1 (0.4)	2 (2.0)
Hyperphosphataemia	0	0	0	2 (4.1)	0	2 (2.0)
Respiratory, thoracic and mediastinal disorders						
Cough	4 (3.8)	2 (3.8)	0	1 (2.0)	4 (1.6)	3 (2.9)

Skin and subcutaneous tissue disorders						
Rash	8 (7.5)	2 (3.8)	5 (3.3)	0	13 (5.1)	2 (2.0)
Pruritus	1 (0.9)	3 (5.7)	3 (2.0)	0	4 (1.6)	3 (2.9)
Rash macular[a]	1 (0.9)	0	2 (1.3)	0	3 (1.2)	0
Rash maculo-papular[a]	1 (0.9)	0	1 (0.7)	0	2 (0.8)	0
Rash erythematous[a]	0	0	0	1 (2.0)	0	1 (1.0)

Note: Percentages are calculated as 100 × (n/N).
a Additional preferred terms related to rash are included in this table.
Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; N = number of subjects in the Safety Population; n = number of subjects within a specific category; TEAE = treatment-emergent adverse event.
Source: Appendix Table 3.1.1 and Appendix Table 3.2.1.

Source: NDA 200327 Module 2.5 Clinical Overview, Table 5.3-2.

***Reviewer comment**: In a response to an Information Request from the Division, the Sponsor also presents the adverse reactions in the Group 1 studies occurring at ≥2% (**Table 21**). The majority of the TEAEs occurred in 1 subject within a treatment group. For ease of comparing the two tables, the new preferred terms and system organ class are highlighted in yellow in the Sponsor's table.*

Additional TEAEs occurring at greater than or equal to 2% in the ceftaroline fosamil arm of the pooled Group 1 pediatric studies which may warrant inclusion in the label include 'abdominal pain', 'gastroenteritis', 'aspartate aminotransferase increased', 'alanine aminotransferase increased', 'headache', 'cough', 'dermatitis diaper' and 'pruritus'.

Table 21 Incidence of Common (≥ 2%) Treatment-emergent Adverse Events by System Organ Class and Preferred Term Across the Completed Active-controlled, Parallel-group Clinical Studies in Pediatric Subjects—Safety Population.

System Organ Class *Preferred Term*	*ABSSSI Study P903-23*		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106) n (%)	*Comparators (N = 53) n (%)*	*Ceftaroline (N = 151) n (%)*	*Comparators (N = 49) n (%)*	*Ceftaroline (N = 257) n (%)*	*Comparators (N = 102) n (%)*
Subjects with at least 1 TEAE	*51 (48.1)*	*23 (43.4)*	*67 (44.4)*	*26 (53.1)*	*118 (45.9)*	*49 (48.0)*
Blood and lymphatic system disorders						
Anaemia	0	0	6 (4.0)	1 (2.0)	6 (2.3)	1 (1.0)
Eosinophilia	5 (4.7)	1 (1.9)	1 (0.7)	0	6 (2.3)	1 (1.0)
Thrombocytosis	0	0	3 (2.0)	4 (8.2)	3 (1.2)	4 (3.9)
Bandaemia	0	0	0	1 (2.0)	0	1 (1.0)
Cardiac disorders						
Bradyarrhythmia	0	0	0	1 (2.0)	0	1 (1.0)
Gastrointestinal disorders						
Diarrhoea	8 (7.5)	8 (15.1)	12 (7.9)	2 (4.1)	20 (7.8)	10 (9.8)
Vomiting	7 (6.6)	8 (15.1)	6 (4.0)	4 (8.2)	13 (5.1)	12 (11.8)
Nausea	5 (4.7)	0	3 (2.0)	1 (2.0)	8 (3.1)	1 (1.0)
Abdominal pain	3 (2.8)	1 (1.9)	3 (2.0)	1 (2.0)	6 (2.3)	2 (2.0)
Constipation	2 (1.9)	1 (1.9)	1 (0.7)	1 (2.0)	3 (1.2)	2 (2.0)
Enteritis	0	0	0	1 (2.0)	0	1 (1.0)
General disorders and administration site conditions						
Pyrexia	4 (3.8)	0	4 (2.6)	2 (4.1)	8 (3.1)	2 (2.0)
Device occlusion	0	0	1 (0.7)	1 (2.0)	1 (0.4)	1 (1.0)
Oedema peripheral	0	0	0	1 (2.0)	0	1 (1.0)
Infections and infestations						
Upper respiratory tract infection	5 (4.7)	1 (1.9)	1 (0.7)	2 (4.1)	6 (2.3)	3 (2.9)
Gastroenteritis	1 (0.9)	0	3 (2.0)	1 (2.0)	4 (1.6)	1 (1.0)
Bronchitis	1 (0.9)	0	2 (1.3)	1 (2.0)	3 (1.2)	1 (1.0)
Rhinitis	0	1 (1.9)	2 (1.3)	1 (2.0)	2 (0.8)	2 (2.0)
Conjunctivitis	0	0	1 (0.7)	1 (2.0)	1 (0.4)	1 (1.0)
Oral fungal infection	0	0	1 (0.7)	1 (2.0)	1 (0.4)	1 (1.0)
Otitis media	0	0	1 (0.7)	3 (6.1)	1 (0.4)	3 (2.9)
Viral upper respiratory tract infection	0	0	1 (0.7)	2 (4.1)	1 (0.4)	2 (2.0)
Gastroenteritis rotavirus	0	0	0	1 (2.0)	0	1 (1.0)
Gastroenteritis viral	0	0	0	1 (2.0)	0	1 (1.0)
Lower respiratory tract infection viral	0	0	0	1 (2.0)	0	1 (1.0)
Varicella	0	1 (1.9)	0	1 (2.0)	0	2 (2.0)
Injury, poisoning and procedural complications						

Infusion related reaction	1 (0.9)	0	1 (0.7)	1 (2.0)	2 (0.8)	1 (1.0)
Arthropod bite	0	2 (3.8)	0	0	0	2 (2.0)
Investigations						
Aspartate aminotransferase increased	1 (0.9)	0	4 (2.6)	1 (2.0)	5 (1.9)	1 (1.0)
Alanine aminotransferase increased	1 (0.9)	1 (1.9)	3 (2.0)	2 (4.1)	4 (1.6)	3 (2.9)
Transaminases increased	0	0	2 (1.3)	1 (2.0)	2 (0.8)	1 (1.0)
Blood lactate dehydrogenase increased	0	0	1 (0.7)	1 (2.0)	1 (0.4)	1 (1.0)
Blood pressure diastolic decreased	0	0	0	1 (2.0)	0	1 (1.0)
Oxygen saturation decreased	0	0	0	1 (2.0)	0	1 (1.0)
Metabolism and nutrition disorders						
Decreased appetite	2 (1.9)	0	1 (0.7)	1 (2.0)	3 (1.2)	1 (1.0)
Hypoalbuminaemia	0	0	2 (1.3)	1 (2.0)	2 (0.8)	1 (1.0)
Hypocalcaemia	0	0	1 (0.7)	2 (4.1)	1 (0.4)	2 (2.0)
Fluid retention	0	0	0	1 (2.0)	0	1 (1.0)
Hyperglycaemia	0	0	0	1 (2.0)	0	1 (1.0)
Hyperphosphataemia	0	0	0	2 (4.1)	0	2 (2.0)
Hypokalaemia	0	0	0	1 (2.0)	0	1 (1.0)
Hypophagia	0	0	0	1 (2.0)	0	1 (1.0)
Nervous system disorders						
Headache	3 (2.8)	1 (1.9)	3 (2.0)	0	6 (2.3)	1 (1.0)
Lethargy	0	0	0	1 (2.0)	0	1 (1.0)
Reproductive system and breast disorders						
Vulvovaginal erythema	0	0	0	1 (2.0)	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders						
Cough	4 (3.8)	2 (3.8)	0	1 (2.0)	4 (1.6)	3 (2.9)
Hypoxia	0	0	0	1 (2.0)	0	1 (1.0)
Nasal congestion	0	0	0	1 (2.0)	0	1 (1.0)
Pneumothorax	0	0	0	1 (2.0)	0	1 (1.0)
Pulmonary oedema	0	0	0	1 (2.0)	0	1 (1.0)
Pulmonary pneumatocele	0	0	0	1 (2.0)	0	1 (1.0)
Pulmonary thrombosis	0	0	0	1 (2.0)	0	1 (1.0)
Respiratory distress	0	0	0	1 (2.0)	0	1 (1.0)

Skin and subcutaneous tissue disorders						
Rash	8 (7.5)	2 (3.8)	5 (3.3)	0	13 (5.1)	2 (2.0)
Dermatitis diaper	2 (1.9)	1 (1.9)	3 (2.0)	1 (2.0)	5 (1.9)	2 (2.0)
Pruritus	1 (0.9)	3 (5.7)	3 (2.0)	0	4 (1.6)	3 (2.9)
Urticaria	0	0	3 (2.0)	1 (2.0)	3 (1.2)	1 (1.0)
Eczema	1 (0.9)	0	0	1 (2.0)	1 (0.4)	1 (1.0)
Dermatitis	0	0	0	1 (2.0)	0	1 (1.0)
Dermatitis atopic	0	0	0	1 (2.0)	0	1 (1.0)
Rash erythematous	0	0	0	1 (2.0)	0	1 (1.0)
Red man syndrome	0	1 (1.9)	0	1 (2.0)	0	2 (2.0)
Rash macular[a]	1 (0.9)	0	2 (1.3)	0	3 (1.2)	0
Rash maculo-papular[a]	1 (0.9)	0	1 (0.7)	0	2 (0.8)	0

Note: Percentages are calculated as 100 × (n/N).
a Additional preferred terms related to rash are included in this table (incidence less than 2%)
Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; N = number of subjects in the Safety Population; n = number of subjects within a specific category; TEAE = treatment-emergent adverse event.
Source: Appendix Table 3.1.1 and Appendix Table 3.2.1a

Source: NDA 200327 Module 1.11.2 Safety Information Amendment, Table 5.3-2a.

In the Group 1 studies, there were 7 subjects at sites where financial disclosures could not be obtained. At site 702, 2 of 6 subjects experienced non-serious TEAEs (irritability and vomiting). The one subject enrolled at site 804 did not experience a TEAE.

Across age cohorts, the percentage of subjects who had at least 1 TEAE was similar between ceftaroline and comparator groups (**Table 22**). The types of TEAEs across age cohorts were similar; however small sample sizes in each age cohort preclude definitive conclusions from being made. Please see the Sponsor's Summary of Clinical Safety Appendix Table 3.1.1.2 for additional details. TEAEs by sex and race are described in **Section 8.5**.

Table 22 Incidence of Subjects With at Least One Treatment-emergent Adverse Event Across Age Cohorts in Active-controlled Pediatric Studies—Safety Population.

	ABSSSI Study P903-23		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
Age Cohort	*Ceftaroline n (%)*	*Comparators n (%)*	*Ceftaroline n (%)*	*Comparators n (%)*	*Ceftaroline n (%)*	*Comparators n (%)*
12 years to < 18 years	6 (26.1)	4 (30.8)	7 (53.8)	2 (50.0)	13 (36.1)	6 (35.3)
6 years to < 12 years	17 (47.2)	7 (46.7)	15 (45.5)	3 (27.3)	32 (46.4)	10 (38.5)
24 months to < 6 years	11 (47.8)	4 (33.3)	34 (44.7)	17 (68.0)	45 (45.5)	21 (56.8)
2 months to < 24 months	17 (70.8)	8 (61.5)	11 (37.9)	4 (44.4)	28 (52.8)	12 (54.5)

Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia

Source: Appendix Table 3.1.1.2.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety, Table 5.1.2.1.3-1.

GROUP 2 STUDIES

Study P903-21

In study P903-21, TEAEs were reported in 43.4% of subjects (23 of 53) (**Table 23**). Three SAEs reported in 3 (5.7%) subjects are described in **Section 8.3.5** (**Subject 01121005**, Cohort 1: rash; **Subject 02021003**, Cohort 3: tremor; **Subject 01021004**, Cohort 5: anemia neonatal).

The most common SOC for TEAEs was Investigations (6 [11.3%] subjects) (**Table 23**). The most common TEAEs included ALT increased, AST increased, blood creatine phosphokinase (CPK) increased, blood LDH increased, prothrombin time prolonged, and hyperbilirubinemia (2 subjects each). No subjects discontinued due to an AE.

Most TEAEs were categorized as mild (56.8%) or moderate (31.8%) in severity with 5 (11.4%) of the TEAEs determined to be severe.

Table 23 Incidence of Treatment-Emergent Adverse Events by Cohort, System Organ Class, and Preferred Term—Safety Population – Group 2 Studies.

System Organ Class Preferred Term	*Cohort 1 (N = 10)*	*Cohort 2 (N = 8)*	*Cohort 3 (N = 12)*	*Cohort 4 (N = 12)*	*Cohort 5 (N = 11)*	*All Subjects[a] (N = 53)*
Subject with at least 1 TEAE, n (%)	**3 (30)**	**0**	**7 (58.3)**	**7 (58.3)**	**6 (54.5)**	**23 (43.4)**
Investigations	**0**	**0**	**1 (8.3)**	**4 (33.3)**	**1 (9.1)**	**6 (11.3)**
ALT increased	0	0	0	2 (16.7)	0	2 (3.8)
AST increased	0	0	0	2 (16.7)	0	2 (3.8)
Blood CPK increased	0	0	0	2 (16.7)	0	2 (3.8)
Blood LDH increased	0	0	0	2 (16.7)	0	2 (3.8)
PT prolonged	0	0	0	2 (16.7)	0	2 (3.8)
aPTT prolonged	0	0	0	1 (8.3)	0	1 (1.9)
Blood phosphorus increased	0	0	0	0	1 (9.1)	1 (1.9)
GGT increased	0	0	1 (8.3)	0	0	1 (1.9)
INR increased	0	0	0	1 (8.3)	0	1 (1.9)
Neutrophil count decreased	0	0	0	0	1 (9.1)	1 (1.9)
General disorders and administration site conditions	**2 (20.0)**	**0**	**2 (16.7)**	**0**	**0**	**4 (7.5)**
Device occlusion	0	0	1 (8.3)	0	0	1 (1.9)
Infusion site pain	1 (10.0)	0	0	0	0	1 (1.9)
Pain	1 (10.0)	0	0	0	0	1 (1.9)
Pyrexia	0	0	1 (8.3)	0	0	1 (1.9)

System Organ Class Preferred Term	*Cohort 1 (N = 10)*	*Cohort 2 (N = 8)*	*Cohort 3 (N = 12)*	*Cohort 4 (N = 12)*	*Cohort 5 (N = 11)*	*All Subjects[a] (N = 53)*
Blood and lymphatic system disorders	**0**	**0**	**0**	**2 (16.7)**	**1 (9.1)**	**3 (5.7)**
Anemia	0	0	0	1 (8.3)	0	1 (1.9)
Anemia neonatal	0	0	0	0	1 (9.1)	1 (1.9)
Coagulopathy	0	0	0	1 (8.3)	0	1 (1.9)
Injury, poisoning and procedural complications	**0**	**0**	**2 (16.7)**	**1 (8.3)**	**0**	**3 (5.7)**
Excoriation	0	0	0	1 (8.3)	0	1 (1.9)
Overdose	0	0	1 (8.3)	0	0	1 (1.9)
Procedural pain	0	0	1 (8.3)	0	0	1 (1.9)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (8.3)**	**0**	**2 (18.2)**	**3 (5.7)**
Atelectasis	0	0	0	0	1 (9.1)	1 (1.9)
Respiratory acidosis	0	0	0	0	1 (9.1)	1 (1.9)
Tachypnea	0	0	1 (8.3)	0	0	1 (1.9)
Gastrointestinal system disorders	**1 (10.0)**	**0**	**1 (8.3)**	**0**	**0**	**2 (3.8)**
Abdominal pain	1 (10.0)	0	0	0	0	1 (1.9)
Diarrhea	0	0	1 (8.3)	0	0	1 (1.9)
Nausea	1 (10.0)	0	0	0	0	1 (1.9)
Perianal erythema	0	0	1 (8.3)	0	0	1 (1.9)
Hepatobiliary disorders	**0**	**0**	**0**	**1 (8.3)**	**1 (9.1)**	**2 (3.8)**
Hyperbilirubinemia	0	0	0	1 (8.3)	1 (9.1)	2 (3.8)
Infections and infestations	**0**	**0**	**1 (8.3)**	**0**	**1 (9.1)**	**2 (3.8)**
Bronchiolitis	0	0	1 (8.3)	0	0	1 (1.9)
Candidiasis	0	0	0	0	1 (9.1)	1 (1.9)
Metabolism and nutrition disorders	**0**	**0**	**1 (8.3)**	**1 (8.3)**	**0**	**2 (3.8)**
Alkalosis hypochloremic	0	0	1 (8.3)	0	0	1 (1.9)
Hypoalbuminemia	0	0	0	1 (8.3)	0	1 (1.9)

System Organ Class Preferred Term	*Cohort 1 (N = 10)*	*Cohort 2 (N = 8)*	*Cohort 3 (N = 12)*	*Cohort 4 (N = 12)*	*Cohort 5 (N = 11)*	*All Subjects[a] (N = 53)*
Skin and subcutaneous tissue disorders	**1 (10.0)**	**0**	**0**	**1 (8.3)**	**0**	**2 (3.8)**
Dry Skin	0	0	0	1 (8.3)	0	1 (1.9)
Rash	1 (10.0)	0	0	0	0	1 (1.9)
Congenital, familial and genetic disorders	**0**	**0**	**1 (8.3)**	**0**	**0**	**1 (1.9)**
Coarctation of the aorta	0	0	1 (8.3)	0	0	1 (1.9)
Nervous system disorders	**0**	**0**	**1 (8.3)**	**0**	**0**	**1 (1.9)**
Tremor	0	0	1 (8.3)	0	0	1 (1.9)

Notes: MedDRA version 15.1 was used to code adverse events. Cohorts: 1 = children ages ≥ 6 years to < 12 years; 2 = children ages ≥ 24 months to < 6 years; 3 = infants and toddlers ages ≥ 28 days to < 24 months; 4 = term neonates ages < 28 days; 5 = preterm (defined as gestational age 32 - 37 weeks) neonates ages < 28 days. Subjects reporting a particular adverse event (preferred term) more than once were counted only once by preferred term and System Organ Class. Percentages were calculated as 100 × (n/N).
Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyltransferase; INR = international normalized ratio; LDH = lactate dehydrogenase; N = number of subjects in the Safety Population; n = number of subjects in the specific category; PT = prothrombin time.
a All Subjects = subjects pooled across all age cohorts.
Source: Table 14.3.3.2.

Source: NDA 200327 Module 5.0 Clinical Study Report, Table 12.2.2-1.

Study P903-15

In study P903-15, 55.6% of subjects (5 of 9) had a TEAE (**Subject 0001-15004, 0001-15005, 0001-15007, 0003-15001, 0004-15001**) (**Table** 24). None of the TEAEs were considered SAEs or resulted in discontinuation from the study. One subject (**0003-15001**) was prematurely discontinued from study drug after receiving about 80% of the planned dose) because of a TEAE, extravasation at the infusion site. No subjects had a TEAE that was severe.

There was one subject (**0001-15007**) with a TEAE of ECG prolonged QT interval. The subject was admitted to hospital for appendicitis, had an onset on Day 2 at about 24 hours after the start of infusion with a QTcB of 446 msec and a QTcF of 413 msec (heart rate of 94 bpm). At baseline, predose, and at the end of infusion of ceftaroline fosamil, the subject had QTcB values of 442, 442, and 444 msec, respectively, QTcF values of 404, 404, and 401 msec, respectively, and ventricular heart rates of 104, 104, and 110 bpm, respectively. The ECG prolonged QT interval was not assessed after Study Day 2. No ECG values for this subject met potentially clinically significant (PCS) criteria, and no other TEAEs were reported for this subject.

Table 24 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Severity, and Relationship to Ceftaroline—Safety Population – Study P903-15.

Adverse Event by SOC and Preferred Term[a]	*Total N = 9 n (%)*				
	Any TEAE	*Severity*[b]		*Relationship*[c]	
		Mild	**Moderate**	**Unrelated**	**Related**
Subjects with ≥ 1 TEAE	5 (55.6)	3 (33.3)	2 (22.2)	2 (22.2)	3 (33.3)
Cardiac disorders	1 (11.1)	1 (11.1)	0	0	1 (11.1)
Extrasystoles	1 (11.1)	1 (11.1)	0	0	1 (11.1)
Gastrointestinal disorders	2 (22.2)	1 (11.1)	1 (11.1)	1 (11.1)	1 (11.1)
Constipation	1 (11.1)	1 (11.1)	0	1 (11.1)	0
Vomiting	1 (11.1)	0	1 (11.1)	0	1 (11.1)
General disorders and administrative site conditions	1 (11.1)	0	1 (11.1)	1 (11.1)	0
Infusion site extravasation	1 (11.1)	0	1 (11.1)	1 (11.1)	0
Investigations	1 (11.1)	1 (11.1)	0	0	1 (11.1)
ECG prolonged QT	1 (11.1)	1 (11.1)	0	0	1 (11.1)
Musculoskeletal and connective tissue disorders	1 (11.1)	0	1 (11.1)	1 (11.1)	0
Arthralgia	1 (11.1)	0	1 (11.1)	1 (11.1)	0
Pathological fracture	1 (11.1)	1 (11.1)	0	1 (11.1)	0
Respiratory, thoracic, and mediastinal disorders	1 (11.1)	1 (11.1)	0	1 (11.1)	0
Nasal dryness	1 (11.1)	1 (11.1)	0	1 (11.1)	0

Abbreviation: AE = adverse event; ECG = electrocardiogram; QT = time between the start of the Q wave and the end of the T wave; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

a Version 11.1 of MedDRA was used to code TEAEs.

b Subjects reporting a particular TEAE by preferred term more than once are counted only once by preferred term SOC and at the highest severity.

c Subjects reporting a particular TEAE by preferred term more than once are counted only once by preferred term and SOC and at the strongest relationship. Related TEAEs included TEAEs that were considered possibly or probably related to ceftaroline by the Investigator.

Source: Table 14.3.3.1, Table 14.3.3.2, Table 14.3.3.3.

Source: NDA 200327 Module 5.0 Study P903-15 Clinical Study Report, Table 12.2.2-1.

COMPARISON WITH ADULT PHASE 3 STUDIES

In the active-controlled pooled adult Phase 3 studies, the most common TEAEs (≥ 2% of subjects in any treatment group) in subjects receiving ceftaroline fosamil were diarrhea (n = 60 [4.6%]), headache (n = 57 [4.4%]), and nausea (n = 55 [4.2%]) (**Table 25**).

Table 25 Incidence of Common ≥ 2% Treatment-emergent Adverse Events by System Organ Class and Preferred Term Across the Completed Active-controlled Phase 3 Clinical Studies in Adult Subjects—Safety Population.

System Organ Class Preferred Term	*cSSSI (06, 07)*		*CABP (08, 09)*		*Pooled Phase 3 Studies (06, 07, 08, 09)*	
	Ceftaroline (N = 692) n (%)	*Vancomycin plus Aztreonam (N = 686) n (%)*	*Ceftaroline (N = 613) n (%)*	*Ceftriaxone (N = 615) n (%)*	*Ceftaroline (N = 1305) n (%)*	*Pooled Comparators (N = 1301) n (%)*
Subjects with at Least 1 TEAE	**309 (44.7)**	**326 (47.5)**	**288 (47.0)**	**281 (45.7)**	**597 (45.7)**	**607 (46.7)**
Gastrointestinal disorders						
Diarrhoea	34 (4.9)	26 (3.8)	26 (4.2)	16 (2.6)	60 (4.6)	42 (3.2)
Nausea	41 (5.9)	35 (5.1)	14 (2.3)	14 (2.3)	55 (4.2)	49 (3.8)
Constipation	18 (2.6)	18 (2.6)	9 (1.5)	6 (1.0)	27 (2.1)	24 (1.8)
Vomiting	20 (2.9)	18 (2.6)	7 (1.1)	2 (0.3)	27 (2.1)	20 (1.5)
General disorders and administration site conditions						
Pyrexia	9 (1.3)	16 (2.3)	4 (0.7)	5 (0.8)	13 (1.0)	21 (1.6)
Metabolism and nutrition disorders						
Hypokalaemia	10 (1.4)	15 (2.2)	14 (2.3)	15 (2.4)	24 (1.8)	30 (2.3)
Nervous system disorders						
Headache	36 (5.2)	31 (4.5)	21 (3.4)	9 (1.5)	57 (4.4)	40 (3.1)
Dizziness	14 (2.0)	8 (1.2)	3 (0.5)	2 (0.3)	17 (1.3)	10 (0.8)
Psychiatric disorders						
Insomnia	17 (2.5)	17 (2.5)	19 (3.1)	14 (2.3)	36 (2.8)	31 (2.4)
Skin and subcutaneous tissue disorders						
Pruritus	24 (3.5)	56 (8.2)	1 (0.2)	3 (0.5)	25 (1.9)	59 (4.5)
Rash	22 (3.2)	17 (2.5)	2 (0.3)	2 (0.3)	24 (1.8)	19 (1.5)
Pruritus generalised	15 (2.2)	19 (2.8)	0	0	15 (1.1)	19 (1.5)
Vascular disorders						
Hypertension	9 (1.3)	10 (1.5)	14 (2.3)	16 (2.6)	23 (1.8)	26 (2.0)
Phlebitis	3 (0.4)	5 (0.7)	17 (2.8)	13 (2.1)	20 (1.5)	18 (1.4)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; TEAE = treatment-emergent adverse event.
Source: Module 5.3.5.3 [ISS], Table 8.3.1.1-1 in the original NDA [Sequence 0000].

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety, Table 5.1.2.2-1.

Selected TEAEs by SOC are compared between the pediatric Group 1 studies and the pooled adult Phase 3 studies (selected TEAEs ≥2% [**Appendix 13.16**].

In both pediatric and adult subjects, TEAEs most commonly occurred in the gastrointestinal disorders, as well as skin and subcutaneous disorders SOCs. In the Group 1 pediatric studies,

the incidence of diarrhea and vomiting was higher in both the ceftaroline and comparator arms when compared to adults (**Appendix 13.16**). In addition, the incidence of rash was higher in the ceftaroline arm of the pediatric studies (5.1%) than that observed in ceftaroline arm of the pooled adult Phase 3 studies (1.8%).

Reviewer comment: *Although the incidence of diarrhea, vomiting and rash are higher in the ceftaroline arm of the pooled Group 1 pediatric studies when compared to the ceftaroline arm of the pooled Phase 3 adult studies, it is difficult to conclude that there is a true increased incidence with small sample sizes and differences in trial design. In addition, the current label lists diarrhea, vomiting and rash as adverse reactions occurring in ≥ 2 % of patients receiving ceftaroline in the pooled Phase 3 adult clinical trials.[1] It appears that the pediatric population shares a similar adverse event profile to adult exposed to ceftaroline fosamil.*

8.3.9. Laboratory Findings

Please see **Section 8.3.7 Significant Adverse Events** for laboratory results related to Direct Coombs' Test Seroconversion/ Hemolytic Anemia, Development of Drug-Resistant Bacteria, Bone marrow suppression (Agranulocytosis, leukopenia, neutropenia), Eosinophlic pneumonia, Renal Failure and Drug-induced liver injury.

GROUP 1 STUDIES

In the Group 1 studies, potentially clinically significant (PCS) hematology and serum chemistry) values were similar and low in the ceftaroline and comparator groups. In addition, shifts in hematology and serum chemistry parameters in pediatric studies from normal to low and from normal to high occurred with a similar frequency in the ceftaroline andcomparator groups. No subjects met potential Hy's law criteria.

GROUP 2 STUDIES

Study P903-21

In Study P903-21, there were 7 PCS laboratory abnormalities in 5 subjects, all in the youngest age cohorts (Cohort 4, n=3; Cohort 5, n=2).

Reviewer comment: *It appears that the children receiving ceftaroline fosamil and experiencing PCS laboratory abnormalities had multiple medical co-morbidities. The role of ceftaroline fosamil in contributing to the TEAEs is difficult to discern.*

Study P903-15

In Study P903-15, one subject (**0004-15001**) had a hematology value that met PCS criteria, a long activated PTT. The subject had a major trauma 7 days before infusion of ceftaroline fosamil and had received plasma, red blood cells, albumin, and platelets for blood loss from the trauma and subsequent surgery. The subject's PTT at baseline was 40.0 seconds. On Study Day 2, the subject had an activated PTT of 91.0 seconds that was 127.5% above baseline.

COMPARISON WITH ADULT PHASE 3 STUDIES

The incidence of PCS hematology and chemistry laboratory results from the active-controlled Phase 3 studies in adult subjects were similar to the pediatric Group 1 studies. PCS decreases in hematocrit, hemoglobin, and RBC count were low and occurred at similar frequencies in the ceftaroline and comparator groups (n = 12 [1.2%], n = 16 [1.5%], 1.4%, respectively, vs n = 17 [1.7%], n = 21 [1.9%], and 2.3%, respectively).

Reviewer comment: *There are no new laboratory findings which represent new safety signals for ceftaroline fosmail in the pediatric population.*

8.3.10. Vital Signs

In both the Group 1 and Group 2 pediatric studies, mean changes in vital signs were unremarkable and similar between treatment groups. For descriptive statistics of vital sign parameters by age cohort in the Group 1 studies, please refer to Appendix Table 5.1.1.1 in the Summary of Clinical Safety.

8.3.11. Electrocardiograms (ECGs)

Electrocardiograms were not performed for the pediatric clinical studies.

8.3.12. QT

The Sponsor conducted Study P903-05, a thorough QT study (TQT), and submitted results to support the original NDA application. The study was reviewed by the FDA Interdisciplinary Review Team for QT studies. No significant QT prolongation effect of ceftaroline 1500 mg was detected in this TQT study. Please refer to relevant discipline-specific reviews for the original NDA for details.

In the single dose PK study, P903-15, there was one subject with a TEAE of ECG prolonged QT interval which did not meet criteria for PCS. Please see **Section 8.3.8** for additional details.

8.3.13. Immunogenicity

Please see **Section 8.3.8** for additional details. Hypersensitivity reactions are a cephalosporin 'class effect'. Hypersensitivity reactions are listed in the Warnings and Precautions section of the label for ceftaroline fosamil.

8.4. Analysis of Submission-Specific Safety Issues

Please see **Section 8.3.7 Significant Adverse events**.

8.5. Safety Analyses by Demographic Subgroups

Age

In the Group 1 studies, subjects were distributed amongst all 4 age cohorts, with similar percent enrollment in the ceftaroline fosamil and comparator arms for each cohort (**Section 8.2.2**). However, given the small number of subjects enrolled in each cohort, particularly in the comparator arm, it is difficult to draw conclusions about age-group specific risk factors for adverse events associated with ceftaroline fosamil use.

Sex

In the Group 1 studies, the percentage of males and females was similar in the ceftaroline (female 116 [45.1%]; male 141 [54.9%]) and comparator arms (female 44 [43.1%]; male 58 [56.9%]). The extent of exposure was similar between the sexes in each treatment arm. In the ceftaroline fosamil arm, a similar percentage of males and females in the ceftaroline group had at least 1 TEAE (males: n = 64 [45.4%]; females: n = 54 [46.6%]). This is in contrast to the comparator group where a higher percentage of female subjects (n = 26 [59.1%]) had at least 1 TEAE compared with male subjects (n = 23 [39.7%]). There was no discernible pattern in the incidence of specific TEAEs by sex in this small safety population. In addition, there was no discernible pattern in the rate of discontinuation of study drug due to TEAEs between female and male subjects. Please see Appendix **Tables 3.1.1.1** and **3.5.1.1** in the Summary of Clinical Safety for details regarding the number and percentage of subjects with TEAEs in each treatment group tabulated by SOC and PT, and the incidence of AEs leading to discontinuation of study drug, respectively.

Race

In the Group 1 studies, the percentage of non-White children enrolled was equally low in both arms (ceftaroline 8.2% [21/257]; comparator 6.9% [7/102]). Because of the small number of non-White children enrolled in the pooled Group 1 studies, it is difficult to draw conclusions about race-group specific risk factors for adverse events associated with ceftaroline fosamil use.

8.6. Specific Safety Studies/Clinical Trials

This section is not applicable for the current submission.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

This section is not applicable for the current submission. Please refer to the original NDA discipline specific reviews for additional details.

8.7.2. Human Reproduction and Pregnancy

Clinical data for ceftaroline exposure in pregnant women are limited. There are no adequate and well-controlled studies in pregnant women.

In a review of all fourteen postmarketing safety reports submitted since original NDA approval, there was one report (SD414 Safety Report-13) with a case of "exposure during pregnancy". No details of the case are provided.

A literature search revealed one report of ceftaroline use in a pregnant woman with cystic fibrosis and multiple drug allergies.[12] In her twelfth week of pregnancy, the woman underwent a 12 step drug desensitization procedure with ceftaroline over 5 hours. The patient tolerated the desensitization procedure and completed 14 days of intravenous ceftaroline (600 milligrams twice daily) without complications. The patient returned to her baseline pulmonary status and gave birth to a full-term healthy male 6 months after her admission.

Please refer to the original Pharmacology Toxicology NDA review by Amy Ellis, PhD for additional details regarding preclinical development and reproductive studies.

Reviewer comment: *Penicillins and cephalosporins are often considered first line antibiotics to use in pregnant women.[13] Cephalosporins are frequently thought to be safe to the fetus. For example, a population based case-control study showed that there was no detectable human teratogenic potential of oral cephalexin and cefuroxime when used during pregnancy.[14] It should be noted that adverse events of immune hemolytic reactions in pregnant women have*

been reported with second and third generation cephalosporins, such as cefotetan. Direct Coombs' test seroconversion is already listed in the Warnings and Precautions section of the ceftaroline label.

8.7.3. Pediatrics and Assessment of Effects on Growth

This section is not applicable for the current submission. Both supplement reviews (S-16 and S-17) evaluate pediatric indications.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no cases of ceftaroline fosamil overdose in the pooled Group 1 pediatric studies.

Please see the original NDA clinical review by Ariel Porcalla, MD, MPH and Neil Rellosa, MD for additional details.

Reviewer comment: *Treatment with cephalosporins may be associated with seizures, particularly in healthy patients who receive an overdose, or in patients with renal impairment when the dose was not reduced. Ceftaroline can be removed by hemodialysis.*

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

The Periodic Adverse Event Report (PADER) from 29 October 2014 to 28 October 2015 reported 9 of 41 (22%) cases of neutropenia/leukopenia. In addition, there was a similar percentage (18/83 [22%]) of neutropenia/leukopenia cases in the PADER covering 29 October 2013 to 28 October 2014. Neutropenia is a labeled event; however leukopenia is not. In the PADER ending 28 October 2015, the Sponsor reports that the marketing authorization holder (not specified) determined that leukopenia will be added to the USPI.

In all spontaneous post-marketing reports since March 31, 2015, the Sponsor describes 4 patients with 8 adverse events where ceftaroline fosamil was administered to pediatric patients under the age of 18 years . Two of these AEs were considered serious, 'eosinophilia' and 'neutropenia'.

The Sponsor submitted an Annual Report (NDA 200327 SD 413) on 22 December 2014 where eosinophilic pneumonia associated with ceftaroline fosamil use was cited in three abstracts in the listing of clinical studies. Eosinophilic pneumonia is not an adverse reaction listed in the current ceftaroline fosamil label. Please see **Section 8.3.7 Significant Adverse Events** for

additional details.

Reviewer comment: *In two consecutive PADERS, neutropenia/leukopenia was noted to occur at a rate of 22% amongst spontaneously reported cases. Neutropenia is currently in section 6.4 of the label (Other Adverse Reactions Observed During Clinical Trials of Teflaro).*
A FAERS search regarding the association of ceftaroline fosamil with neutropenia and leukopenia is ongoing with the Office of Surveillance and Epidemiology (formal consult 21 October 2014). Both neutropenia and leukopenia are known to occur with cephalosporin drug treatment.

This reviewer reccomends the inclusion of leukopenia in the Post-marketing adverse events section of the label.

Note that on 31 August 2015, FDA approved the inclusion of the adverse reaction of 'agranulocytosis' in the Postmarketing Experience subsection (6.2) of the ceftaroline fosamil label. In the reported post-marketing cases, agranulocystosis or neutropenia with ceftaroline occurred when administered at a higher than recommended dose and/or a longer than recommended duration and/or for an off-label indication.

With regards to post-marketing adverse events identified in children, both 'eosinophilia' and 'neutropenia' are known to occur with cephalosporin treatment, including ceftaroline fosamil.

A FAERS search regarding the association of ceftaroline fosamil with eosinophilic pneumonia is ongoing with the Office of Surveillance and Epidemiology (initial email communications January 2015).

8.8.2. Expectations on Safety in the Postmarket Setting

Routine post-marketing adverse event reporting should capture data regarding adverse events associated with ceftaroline fosamil use.

8.9. Additional Safety Issues From Other Disciplines

None identified at the time of this review.

8.10. Integrated Assessment of Safety

As part of the pediatric development program for ceftaroline fosamil, the Sponsor completed 5 clinical studies. One study was conducted in pediatric subjects with ABSSSI (P903-23), two studies were conducted in pediatric subjects with CABP (P903-31 and P903-24), and two PK studies (P903-15 and P903-21) were conducted.

The safety review was conducted by analyzing the active-controlled studies (Group 1) in the following manner: study P903-23 alone (ABSSSI indication), P903-31 and P903-24 combined (CABP indication) and studies P903-23, P903-31 and P903-24 pooled. The safety results for the PK studies (Group 2), P903-21 and P903-15, were also pooled.

In addition, the following treatment emergent adverse events of interest were evaluated in the Group 1 studies, based on the following:

1. Warnings and Precautions section of the current ceftaroline fosamil label[1] (Hypersensitivity Reactions, Clostridium difficile Associated Diarrhea, Direct Coombs' Test Seroconversion/ Hemolytic Anemia, Development of Drug-Resistant Bacteria)
2. Postmarketing safety concerns (Bone marrow suppression [Agranulocytosis, leukopenia, neutropenia], Eosinophlic pneumonia)
3. Other common areas of clinical concern (Convulsions/ Seizures, Renal Impairment, and Drug-induced Liver Injury).

Overall, the safety profile of ceftaroline fosamil when used in the pediatric population studied (426 subjects enrolled and 421 receiving at least 1 dose of study drug) appears to be similar to that described in the adult population, as well as cephalosporin class in general.

In the Group 1 studies, most TEAEs occurred at a similar incidence in both the ceftaroline fosamil and comparator arms. Rash and Direct Coombs' test seroconversion were two exceptions. Rash occurred at a higher incidence in the ceftaroline fosamil arm versus the comparator (13 [5.1%] versus 2 [2.0%], respectively). Direct Coombs' test seroconversions occurred in a higher percentage of pediatric subjects in the ceftaroline group than in the comparator groups (P903-23 [ceftaroline 17.2%; comparators 4.2%], P903-31 [ceftaroline 17.0%; comparators 2.7%], and P903-24 [ceftaroline 26.1%; comparators 0%]).

Subgroup analyses for sex, race or age cohort did not reveal any safety signals. However, the sample sizes were small and definitive conclusions cannot be made.

Key issues discussed with the review team include:

1. Dosing of ceftaroline fosamil in children: The proposed dosing regimen in children is acceptable. Please see the review by Clinical Pharmacology.

2. Duration of Infusion: Ceftaroline fosamil was first approved to be administered as a 1-hour IV infusion in adults with ABSSSI and CABP. Children in the Group 1 studies received ceftaroline fosamil infused over 60 minutes q8h (Studies P903-23 and P903-31) or over 120 minutes q8h (Study P903-24). In the PK studies, children received ceftaroline fosamil infused as a single dose over 60 minutes (Study P903-15) or as a single dose over 1- to 1.5-hours (Study P903-21). Data from a Phase 1 study (CPT-PK-05) in healthy adult subjects, supported approval of a supplement on 31 August 2015 to allow for ceftaroline fosamil infusion over 5 to 60 minutes in adults. The Sponsor proposes that ceftaroline fosamil can also be administered over 5 to 60 minutes in pediatric patients, although it was not studied.

From a safety perspective, the proposed infusion duration of 5 to 60 minutes is acceptable in the pediatric population, including the 2 month to less than 6 month age cohort. Pre-clinical studies suggest that there is a 20 to 28 fold safety margin for ceftaroline. Adult PK and tolerability study comparing ceftaroline fosamil infusion durations of 5 and 60 minutes did not identify safety concerns. Ceftaroline belongs to the widely used cephalosporin class, where class-specific safety issues are well described.

PK simulations support the use of ceftaroline fosamil with an infusion duration of 5 to 60 minutes. After the 5 minute infusion duration, the C_{max} in children 2 months to less than 6 months was similar to adults, adolescents and pediatric patients 6 months to 2 years. In addition, the C_{max} in children 2 months to less than 6 months is lower than the C_{max} in pediatric patients 2 years to less than 12 years. Finally, the exposure resulting from the proposed dose in children 2 months to less than 6 months is similar to the mean C_{max} observed in single dose PK studies in adults.

3. TEAEs occurring at an incidence of greater than or equal to 2 percent: Adverse reactions occurring at greater than or equal to 3% in subjects receiving ceftaroline fosamil include 'diarrhea', 'nausea', 'vomiting', 'pyrexia' and 'rash'. Additional TEAEs occurring at greater than or equal to 2% in the ceftaroline fosamil arm of the pooled Group 1 pediatric studies which may warrant inclusion in the label include 'abdominal pain', 'gastroenteritis', 'aspartate aminotransferase increased', 'alanine aminotransferase increased', 'headache', 'cough', 'dermatitis diaper' and 'pruritus'.

4. Postmarketing Experience Adverse Reactions - Leukopenia: Although not directly related to the pediatric clinical studies, the Periodic Adverse Drug Event Report (PADER) from 29 October 2014 to 28 October 2015, showed 9 cases of neutropenia/leukopenia (22%).

There was a similar percentage (22%) of neutropenia and leukopenia in the PADER covering 29 October 2013 to 28 October 2014. Neutropenia is currently in section 6.4 of the label (Other Adverse Reactions Observed During Clinical Trials of Teflaro). Leukopenia is not a labelled adverse reaction. A FAERS search regarding the association of ceftaroline fosamil with neutropenia and leukopenia is ongoing with the Office of Surveillance and Epidemiology. Note that on August 31, 2015, FDA approved the inclusion of the adverse reaction of 'agranulocytosis' in the Postmarketing Experience subsection (6.2) of the ceftaroline fosamil label.

Based on the safety review of the submitted data, this reviewer recommends approval of ceftaroline fosamil for use in children 2 months to less than 18 years for the treatment of ABSSSI and CABP caused by relevant susceptible isolates.

9 Advisory Committee Meeting and Other External Consultations

This section is not applicable for the current submission. There was no advisory committee meeting, no external consultation and no engagement with patient stakeholders.

10 Labeling Recommendations

10.1. Prescribing Information

Key changes to the Sponsor's proposed label relevant to Clinical are discussed in this section. Numbers indicate the corresponding section of the label. Please refer to the final approved label which will be completed after this review has been submitted.

1. Indications and Usage

The Sponsor proposes to expand the ABSSSI and CABP indications to include children 2 months to less than 18 years.

Reviewer comment: *This change is acceptable.*

2. Dosage and Administration

The Sponsor proposes pediatric dosing with an infusion duration of 5 to 60 minutes.

The Sponsor's proposed dose of ceftaroline fosamil for patients < 18 years with normal renal

function or mild renal impairment (ie, CrCl > 50 mL/min/1.73 m2) for both ABSSSI and CABP is as follows:

- Children 2 to < 24 months: 8 mg/kg (over 5 to 60 minutes) q8h
- Children 24 months to < 18 years and ≤ 33 kg: 12 mg/kg (over 5 to 60 minutes) q8h
- Children 24 months to < 18 years and > 33 kg: 400 mg (over 5 to 60 minutes) q8h

Reviewer comment: *The proposed dosing regimen is appropriate. The proposed dose suggests a modification from the dose used in the ABSSSI Study P903-23, and CABP Study P903-31. The* (b) (4)

Please see review by Clinical Pharmacology.

The proposed infusion duration of 5 to 60 minutes was not studied in the pediatric population. For reasons outlined previously in the review, an infusion duration of 5 to 60 minutes is acceptable in the pediatric population (2 months to less than 18 years) from a safety and clinical pharmacology perspective.

The Sponsor is not seeking to include the higher doses used in Study P903-24, the complicated CABP Study because the 600 mg q8h ceftaroline fosamil dose regimen is not currently approved in adults.

5. Warnings and Precautions

The Sponsor provides pediatric data regarding Coombs test seroconversion.

Reviewer comment: *Direct Coombs' test seroconversion is a known adverse reaction with ceftaroline fosamil use in the adult population. Direct Coombs' test seroconversion occurred in a higher percentage of pediatric subjects in the ceftaroline group than in the comparator groups. This finding should be noted in the Warnings and Precautions section of the label.*

6. Adverse Reactions

The Sponsor describes adverse reactions from the Group 1 studies occurring at an incidence of greater than or equal to 3%.

Table 6 from the label lists adverse reactions occurring in ≥ 3% of patients receiving Teflaro in the pooled pediatric clinical trials.

Table 6: Adverse Reactions Occurring in ≥ 3% of Patients Receiving Teflaro in the Pooled Pediatric Clinical Trials

Adverse Reactions	Pooled Pediatric Clinical Trials (three trials, one in ABSSSI and two in CABP)	
	Teflaro (N=257)	Pooled Comparators[a] (N=102)
Gastrointestinal Disorders		
Diarrhea	8 %	10 %
Nausea	3 %	1 %
Vomiting	5 %	12 %
General and Administrative Site disorders		
Pyrexia	3%	2 %
Skin and Subcutaneous Tissue Disorders		
Rash	7%	4%

[a] Comparators included vancomycin or cefazolin with or without aztreonam in the ABSSI trial and ceftriaxone alone or ceftriaxone plus vancomycin in the CABP trials

The Sponsor proposes the inclusion of the following adverse events as an additional adverse reaction noted in the pediatric clinical trials: 'alanine aminotransferase increased' and 'pruritus'.

***Reviewer comment**: The Sponsor's proposal to display adverse events at ≥3% in the pediatric population is acceptable.*

Additional TEAEs occurring at greater than or equal to 2% in the ceftaroline fosamil arm of the pooled Group 1 pediatric studies which should be included in the label are ' 'aspartate aminotransferase increased', 'alanine aminotransferase increased', 'headache', (b) (4) *and 'pruritus'.*

In addition, leukopenia should be included in the Postmarketing Experience section of the label.

7. Use in Special Populations - Pregnancy

The Sponsor proposes changes to conform to the new Pregnancy and Lactation Labeling Rule.

***Reviewer comment:** The Sponsor's labelling language will be revised with input from the Pharmacology Toxicology Reviewer, Amy Ellis, PhD and the Associate Director for Labeling, Abimbola O. Adebowale, PhD.*

8.4 Use in Special Populations – Pediatric Use

The Sponsor proposes inclusion of information from the pediatric clinical studies in this section.

14. Clinical Trials

The Sponsor proposes inclusion of efficacy data from the pediatric ABSSSI and CABP trials.

Reviewer comment: *The pediatric ABSSSI (P903-23), CABP (P903-31), and complicated CABP (P903-24) studies were not powered for efficacy. Supportive data will be included in the Clinical Trials section and cross-referenced in the Pediatric Use section of the label.*

10.2. Patient Labeling

This section is not applicable for the current submission. A Medication Guide, patient package insert or instructions for use are not required.

10.3. Nonprescription Labeling

This section is not applicable for the current submission.

11 Risk Evaluation and Mitigation Strategies (REMS)

This section is not applicable for the current submission.

12 Postmarketing Requirements and Commitments

The Sponsor addresses (b) (4) 1692-002, and 1692-003 through individual clinical study reports for studies P903-21, P903-31, P903-24 and P903-23 (**Table 26**). These studies are used to support the current submission. (b) (4) The Division met with the Pediatric Review Committee (PeRC) on 27 April 2016 and considers (b) (4) 1692-002, and 1692-003 fulfilled.

Table 26 Summary of PREA Postmarketing Requirements

Submission Date	PMR	Study
04 December 2013	1692-001	P903-21 (Single dose pediatric PK) CSR submitted (SN 0110).
30 October 2014	1692-002	P903-31 (CABP) CSR submitted (SN 0114).
19 November 2014	1692-002	P903-24 (complicated CABP) CSR submitted (SN 0116).
25 November 2014	1692-003	P903-23 (ABSSSI) CSR submitted (SN 0117).
		(b) (4)

13 Appendices

13.1. References

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13.2. Financial Disclosure

Financial disclosure information was provided for studies P903-23, P903-31, and P903-24, because these studies were used by the Sponsor to establish effectiveness. The Sponsor has adequately disclosed financial arrangements with clinical investigators.

Covered Clinical Study (Name and/or Number): P903-23

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 39 Note: PI change at Site 23, counted as 2 PI for totals and not counted in the sub-investigator count. Total number of sub-investigators: 303		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) Not applicable.
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) Not applicable.
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Cerexa and Astra-Zeneca Financial Disclosure Forms were not collected due to staff oversight. Attempts to obtain the information were unsuccessful. Note to files have been obtained from the sites.		

For Study P903-23, Financial Disclosure information could not be obtained from Principal Investigators and Sub-Investigators at Site Number 702 and 804 (**Table 27**). The Sponsor certifies that they have acted with due diligence to obtain these financial disclosures.

Table 27 Study P903-23 Investigators Whom Financial Disclosures Could Not be Obtained

P903-23: A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Efficacy, and Pharmacokinetics of Ceftaroline Versus Comparator in Pediatric Subjects With Acute Bacterial Skin and Skin Structure Infections			
Site No	**Principal Investigator**	**Sub-Investigators (As listed on Form FDA 1572)**	**Reason Financial Disclosure Could Not Be Obtained**
702	Gustavo Cesar Ezcurra, MD	Debora Lucia Gomez Eduardo Gonzalez Mercedes Heinrich	Cerexa and Astra-Zeneca Financial Disclosure Forms were not collected due to staff oversight. Attempts to obtain the information were unsuccessful.
804	Samuel William Moore, MD	Corne De Vos	Cerexa and Astra-Zeneca Financial Disclosure Forms were not collected due to staff oversight. Attempts to obtain the information were unsuccessful.

Source: NDA 200327 SD478 Module 1.3.4 Financial Certification and Disclosure, Attachment 2 to Form FDA 3454.

Covered Clinical Study (Name and/or Number): P903-31

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 35 Total number of sub-investigators identified: 248		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) Not applicable.
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) Not applicable.
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) Not applicable.

Covered Clinical Study (Name and/or Number): P903-24

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12 Total number of sub-investigators identified: 85 Note: PI change at Site 13, counted as 2 PI for totals and not counted in the sub-investigator count.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) Not applicable.
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) Not applicable.
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) Not applicable.

13.3. Additional Study Design Information – Study P903-23

Table 28 Study P903-23 Schedule of Assessments and Procedures

	Assessment or Procedure	Baseline[1]	Treatment					Follow-up	
			SD 1[2] (Postdose)	SDs 2 and 3	SDs 4 to ≤ 14[3]	EOIV[4]	EOT (PO Only)[5]	TOC[6]	LFU[7]
	ICF and assent[8]	X							
	Verify inclusion/exclusion criteria	X							
Clinical	Medical and surgical history	X							
Clinical	Complete physical examination	X							
Clinical	Prior and concomitant medications[9]	X	X	X	X	X	X	X	X
Clinical	Height (length) and weight	X				X[10]	X[10]	X[10]	
Clinical	Vital signs	X	X	X	X	X	X	X	X[11]
Clinical	ABSSSI site procedures documentation[12]	X	X	X	X	X	X	X	X[11]
Clinical	Pain scale[13]	X	X	X	X	X	X	X	X[11]
Clinical	ABSSSI site examination[14]	X	X	X	X	X	X	X	X[11]
Clinical	Clinical outcome					X[15]	X[15]	X[15]	X[16]
Clinical	AEs and SAEs[17]	X	X	X	X	X	X	X	X
Laboratory	CBC with differential, chemistry panel[18]	X			X[19]	X[20]		X[21]	
Laboratory	Direct Coombs test	X						X	
Laboratory	CRP (with chemistry panel)[18]	X	X[22]			X[20]			
Laboratory	Urine pregnancy test[23]	X						X	
Laboratory	CrCl calculation	X							
Micro	ABSSSI specimen for culture	If clinically indicated[24,11]							
Micro	Blood for culture	X	If clinically indicated[25]						X[11]
PK	PK blood samples[26]			X					
PK	Standard of care CSF samples & matching PK blood samples[26]		X						
	Randomization[27]	X							
	Study drug administration		X	X	X[28]	X	X		

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection; AEs = adverse events; CBC = complete blood count; CrCl = creatinine clearance; CRP = C-reactive protein; CSF = cerebrospinal fluid; EOIV = End-of-Intravenous Study Drug; EOT = End-of-Therapy; ICF = informed consent form; IV = intravenous; LFU = Late Follow-up; Micro = microbiology; PK = pharmacokinetic; PO = by mouth; SAEs = serious adverse events; SD = Study Day(s); TOC = Test-of-Cure.

1. Baseline assessments were to be conducted within 24 hours before first dose of IV study drug.
2. SD 1 was the first day of IV study drug administration; subsequent study days were consecutive calendar days. SD 1 assessments were to be conducted after administration of at least 1 dose of IV study drug.
3. On SDs 4 to ≤ 14, study drug administration was to apply to all subjects and daily assessments (AEs, vital signs, concomitant medications, and signs and symptoms of ABSSSI) were to be conducted for subjects on IV study drug only.
4. EOIV assessments were to be conducted in person, within 24 hours after the last dose of IV study drug. The EOIV assessments were to be conducted in place of the regular study visit (eg, Study Days 4 to ≤ 14) assessments that would have been performed the day of that visit. A subject may have been eligible to switch to PO study drug on or after SD 4 (Section 9.4.2.1); EOIV assessments must have occurred before starting PO study drug.
5. EOT assessments were to be conducted in person within 48 hours after the last dose of PO study drug.
6. TOC assessments were to be conducted in person 8 to 15 days after the last dose of any study drug (IV or PO).
7. LFU assessments were to be conducted 21 to 35 days after the last dose of any study drug (IV or PO). LFU was conducted by telephone for any subject who had not experienced clinical relapse, had no ongoing AEs or SAEs at TOC, or had not developed AEs or SAEs since TOC. If symptoms of relapse or new AEs or SAEs were noted, or at the discretion of the Investigator, the subject was immediately scheduled for an in-person visit.
8. Informed consent was obtained in writing from parent(s) or legally acceptable representative(s) and informed assent from subject (if age appropriate according to local requirements) before initiating any study assessments or procedures.
9. All prior medications taken or received within 14 days before the first dose of IV study drug and all concomitant medications taken or received during the study, including but not limited to, antimicrobials, parenteral nutrition, and blood and blood component transfusions were to be recorded. For children who were being breast fed, all medications taken by the lactating mother for 3 days before first dose of IV study drug through LFU were to be recorded.
10. Only weight was to be recorded.
11. Was not to be performed if LFU was conducted via telephone.
12. Procedures performed on the primary ABSSSI (eg, significant surgical intervention, debridement, incision and drainage) were to be recorded.
13. Blinded Observer: Age-appropriate pain scale was to be used.
14. Blinded Observer: The primary ABSSSI and extent (area) of infection (L = longest length in the head to toe orientation and W = widest side-to-side length perpendicular [90° angle] to L) in centimeters were to be assessed.
15. Blinded Observer: Clinical outcome per Table 9.5.2.2.3–1 (EOIV), Table 9.5.2.2.3–2 (EOT), and Table 9.5.2.2.3–3 (TOC) was to be assessed.
16. Blinded Observer: Clinical relapse per Table 9.5.2.2.3–4 (LFU) was to be assessed.
17. Blinded Observer and Investigator: AEs and SAEs were to be collected from signing of the ICF (and assent form, if applicable) until at least 30 days after the last dose of any study drug (or LFU, whichever was later); study center were to follow unresolved AEs and SAEs at LFU until resolution or stabilization.
18. Refer to Section 9.5.4.4 for a detailed list of laboratory tests. Local safety laboratory tests were to be conducted at additional time points, as clinically indicated.
19. Was to be conducted on Study Day 7 if subject was still on IV study drug at that time.
20. If EOIV occurred within 48 hours after these assessments were performed on Study Day 7, these assessments were not to be repeated.
21. Only to be performed if subject had an abnormal (high/low flag) result on or after EOIV.
22. If a subject was on IV study drug and blood was to be drawn for a standard of care chemistry panel, a test for CRP was to be included.
23. Test was to be conducted if subject was a female who had reached menarche. If a pregnancy test was positive at any time postbaseline, the reporting requirements in Section 9.5.4.3 were to be followed.
24. If clinically indicated, ABSSSI specimens for testing were to be collected.
25. If clinically indicated and not already collected per standard of care, blood for testing was to be obtained; blood cultures were to be repeated upon knowledge of a positive result from any test until sterilization was confirmed.
26. PK and CSF samples were to be collected per instructions in Section 9.5.3.
27. Verification that the subject met all study inclusion criteria and no exclusion criteria before randomization was to occur.
28. Study drug was to be administered.

Source: NDA 200327 Clinical Study Report for P903-23, Table 9.5.1-1, Schedule of Assessments and Procedures.

13.4. Clinical and Microbiological Outcome Definitions - Study P903-23

Table 29 Study P903-23 Clinical Outcomes Categories at the End-of-Intravenous Study Drug

Outcome	*Definition*
Clinical cure	Total resolution of all signs and symptoms of the primary ABSSSI, or improvement of the primary ABSSSI to such extent that no further antimicrobial therapy was necessary
Clinical improvement	Subjects who switched to oral study drug and met all of the following criteria at EOIV: • Afebrile (≤ 38.0°C) for at least 24 hours • Lack of fluctuance (if primary infection was an abscess) • Reduction from baseline in area of erythema of the primary ABSSSI
Clinical failure[a]	Subjects who met any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, which included clinical worsening, lack of clinical progress, or requirement of significant surgical intervention on the primary ABSSSI due to lack of efficacy • Discontinuation of study drug due to an AE and subject required further antimicrobial therapy for the primary ABSSSI • Diagnosis of osteomyelitis > 8 days after randomization • Death in which ABSSSI was contributory
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which ABSSSI was clearly noncontributory • Lost to follow-up • Extenuating circumstances that precluded classification as a cure, improvement, or failure (eg, diagnosis of osteomyelitis within 7 days after randomization)

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection; AE = adverse event; EOIV = End-of-Intravenous study drug; EOT = End-of-Therapy; TOC = Test-of-cure.

a A clinical failure at EOIV was carried forward to EOT and TOC.

Source: NDA 200327 Clinical Study Report for P903-23, Table 9.5.2.2.3-1, Clinical Outcomes Categories at the End-of-Intravenous Study Drug.

Table 30 Study P903-23 Clinical Outcomes Categories at the End-of-Therapy

Outcome	*Definition*
Clinical Cure	Total resolution of all signs and symptoms of the primary ABSSSI, or improvement of the primary ABSSSI to such extent that no further antimicrobial therapy was necessary
Clinical Failure[a]	Subjects who met any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect , which included clinical worsening, lack of clinical progress, or requirement of significant surgical intervention on the primary ABSSSI due to lack of efficacy • Discontinuation of study drug due to an AE and subject required further antimicrobial therapy for the primary ABSSSI • Diagnosis of osteomyelitis > 8 days after randomization • Death in which ABSSSI was contributory
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which ABSSSI was clearly noncontributory • Lost to follow-up • Extenuating circumstances that precluded classification as a cure or failure (eg, diagnosis of osteomyelitis within 7 days after randomization)

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection; AE = adverse event; EOT = End-of-Therapy; TOC = Test-of-cure.

a A clinical failure at EOT was carried forward to TOC.

Source: NDA 200327 Clinical Study Report for P903-23, Table 9.5.2.2.3-2, Clinical Outcomes Categories at the End-of-Therapy.

Table 31 Study P903-23 Clinical Outcomes Categories at Test-of-Cure

Outcome	*Definition*
Clinical Cure	Total resolution of all signs and symptoms of the primary ABSSSI, or improvement of the primary ABSSSI to such extent that no further antimicrobial therapy was necessary
Clinical Failure	Subjects who met any of the following criteria: • Incomplete resolution or worsening of signs and symptoms of ABSSSI that required further antimicrobial therapy • Death in which ABSSSI was contributory • Diagnosis of osteomyelitis > 8 days after randomization
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which ABSSSI was clearly noncontributory • Lost to follow-up • Extenuating circumstances that precluded classification as a cure or failure

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection.

Source: NDA 200327 Clinical Study Report for P903-23, Table 9.5.2.2.3-3, Clinical Outcomes Categories at Test-of-Cure.

Table 32 Study P903-23 Clinical Outcomes Categories at Late Follow-up

Outcome	*Definition*
Sustained Clinical Cure	Continued favorable response, defined as total resolution of all signs and symptoms of the primary ABSSSI, or continued improvement of the infection to such extent that no further antimicrobial therapy was necessary
Clinical Relapse	Subjects who met either of the following criteria: • Reappearance or worsening of signs and symptoms of the primary ABSSSI that required further antimicrobial therapy • Death after TOC in which ABSSSI was contributory
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which ABSSSI was clearly noncontributory • Lost to follow-up • Extenuating circumstances that precluded classification as sustained clinical cure or clinical relapse

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection; LFU = Late Follow-up; TOC = Test-of-cure.
Note: Clinical outcomes at LFU was only assessed in subjects who were considered clinically cured at TOC.

Source: NDA 200327 Clinical Study Report for P903-23, Table 9.5.2.2.3-4, Clinical Outcomes Categories at Late Follow-up.

Microbiologic outcomes categories at Test-of-Cure are summarized in .

Table 33 Study P903-23 Microbiologic Outcomes Categories at Test-of-Cure

Microbiological Outcomes[a]	*Definition*
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Presumed eradication	Source specimen was not available to culture and the subject was assessed as clinical cure
Persistence	Source specimen demonstrated continued presence of the original baseline pathogen
Presumed persistence	Source specimen was not available to culture and the subject was assessed as a clinical failure
Indeterminate	Source specimen was not available to culture and the subject's clinical response was assessed as indeterminate

Abbreviation: TOC = Test-of-Cure.
a For subjects who were clinical failures before TOC, the microbiological outcomes were carried forward to TOC and were determined based on the cultures and/or clinical outcomes at the time of the early clinical failure determination.

Source: NDA 200327 Clinical Study Report for P903-23, Table 9.5.2.3.1-1, Microbiologic Outcomes Categories at Test-of-Cure.

Emergent infections were defined as organisms or pathogens first appearing after baseline. Categories for emergent infections are summarized in .

Table 34 Study P903-23 Categories for Emergent Infections

Infection Category	*Definition*
Colonization	Isolation of new organism(s) not present at baseline from the site of infection in a subject who was assessed as a clinical cure
Superinfection	Isolation of new pathogen(s) not present at baseline from the site of infection during treatment with any study drug (IV or oral), which was associated with emergence or worsening of signs and symptoms of infection
New infection	Isolation of new pathogen(s) not present at baseline from the site of infection after completion of all study drug therapy (IV and oral, or IV alone), which was associated with emergence or worsening of signs and symptoms of infection

Abbreviation: IV = intravenous.

Source: NDA 200327 Clinical Study Report for P903-23, Table 9.5.2.3.2-1, Emergent Infections. Emergent infections were defined as organisms or pathogens first appearing after baseline.

13.5. Additional Results – Study P903-23

Patient Disposition

Table 35 Subject Populations and Reasons for Exclusions, Study P903-23—ITT.

Study Population Reasons for Exclusion[a]	*Ceftaroline (N = 110) n (%)*	*Comparator (N = 53) n (%)*
ITT Population	**110 (100)**	**53 (100)**
MITT Population	**107 (97.3)**	**52 (98.1)**
No study drug taken	3 (2.7)	1 (1.9)
No confirmed ABSSSI[b]	0	0
mMITT Population	**52 (47.3)**	**22 (41.5)**
Not in MITT Population	3 (2.7)	1 (1.9)
No baseline pathogen	57 (51.8)	31 (58.5)
CE Population	**96 (87.3)**	**45 (84.9)**
Not in MITT Population	3 (2.7)	1 (1.9)
Test-of-cure visit out of window	10 (9.1)	7 (13.2)
Received incorrect study drug	2 (1.8)	0
Additional inclusion/exclusion criteria violation[c]	2 (1.8)	2 (3.8)
ME Population	**46 (41.8)**	**17 (32.1)**
Not in CE Population	14 (12.7)	8 (15.1)
Not in mMITT Population	58 (52.7)	31 (58.5)

a Subject 170123002 was randomized to the ceftaroline fosamil group, but received treatment with cefazolin. Data for this subject were included in the randomized treatment group for efficacy analyses (N = 107 for ceftaroline fosamil group; N = 52 for comparator group) and are included by treatment received for safety analyses (N = 106 for ceftaroline fosamil group; N = 53 for comparator group).
b Confirmed ABSSSI was defined as meeting Inclusion Criterion #3 and no violation of Exclusion Criterion #2 or #4.
c Additional criteria include Inclusion Criteria #4 and #5 and Exclusion Criteria #3 and #5.
Abbreviations: ABSSSI = acute bacterial skin and skin structure infection; CE = clinically evaluable; CSR = clinical study report; ITT = intent-to-treat; MITT = modified intent-to-treat; mMITT = microbiological modified intent-to-treat; ME = microbiologically evaluable.
Source: CSR P903-23, Table 10.1-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.1.1-1.

Table 36 Study Drug Completion and Reasons for Premature Discontinuation of Study Drug, Study P903-23—ITT Population.

Subject Status *Reason for Discontinuation/Withdrawal*	*Ceftaroline (N = 110) n (%)*	*Comparator (N = 53) n (%)*
Completed study drug	**100 (90.9)**	**47 (88.7)**
Premature discontinuation of any (IV or oral) study drug	**10 (9.1)**	**6 (11.3)**
Subject randomized, but did not receive drug[a]	3 (2.7)	1 (1.9)
Adverse event	2 (1.8)	2 (3.8)
Request of Sponsor or Investigator	2 (1.8)	0
Withdrew consent	3 (2.7)	0
Lost to follow-up	0	1 (1.9)
Other reasons[b]	0	2 (3.8)
Premature discontinuation of IV study drug	**7 (6.4)**	**4 (7.5)**
Subject randomized, but did not receive drug[a]	3 (2.7)	1 (1.9)
Adverse event	2 (1.8)	1 (1.9)
Withdrew consent	2 (1.8)	0
Other reasons[b]	0	2 (3.8)
Premature discontinuation of oral study drug	**3 (2.7)**	**2 (3.8)**
Adverse event	0	1 (1.9)
Request of Sponsor or Investigator	2 (1.8)	0
Withdrew consent	1 (0.9)	0
Lost to follow-up	0	1 (1.9)

a Randomized subjects who did not receive any study drug were counted as premature withdrawals of IV study drug only.

b In the comparator group, 2 subjects discontinued IV study drug for other reasons as follows. Subject 130423001 was discontinued from study drug and the study after 1 infusion when the site received notification that the subject received oral systemic antibiotics at home (meeting Exclusion Criterion #5), and Subject 131423001 was discontinued from IV study drug treatment on Study Day 3 due to osteomyelitis, but did complete the study.

Abbreviations: CSR = clinical study report; ITT = intent-to-treat; IV = intravenous.

Source: CSR P903-23, Table 10.2-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.1.2.2.1-1.

Table 37 Subject Completion and Reasons for Premature Withdrawal from the Study, Study P903-23—ITT Population.

Subject Status *Reason for Discontinuation/Withdrawal*	*Ceftaroline (N = 110)* *n (%)*	*Comparator (N = 53)* *n (%)*
Completed study	**103 (93.6)**	**48 (90.6)**
Premature withdrawal from study	**7 (6.4)**	**5 (9.4)**
Subject did not meet inclusion/exclusion criteria[a]	0	1 (1.9)
Withdrew consent[b]	5 (4.5)	2 (3.8)
Lost to follow-up	0	2 (3.8)
Other reasons[c]	2 (1.8)	0

a In the comparator group, Subject 130423001 was discontinued from study drug and the study after 1 infusion when the site received notification that the subject received oral systemic antibiotics at home (meeting Exclusion Criterion #5). The reason for discontinuation from study drug was captured as "other," while the reason for discontinuation from the study was captured as "subject did not meet inclusion/exclusion criteria."

b In the ceftaroline group, 2 of the 5 subjects (001923001 and 001923002) withdrew consent prior to dosing and did not receive study drug; 1 subject (004423001) who withdrew consent in the comparator group did not receive study drug. Three subjects in the ceftaroline group (006423002, 180223004, and 007023001) and 1 subject in the comparator group (070723004) withdrew consent after receiving study drug treatment.

c In the ceftaroline group, 2 subjects were withdrawn from the study due to other reasons as follows. Subject 170123003 was prematurely withdrawn from study after 5 days of IV study drug when osteomyelitis was suspected for this subject; although this subject also discontinued study drug due to the osteomyelitis, the reason for study drug discontinuation was captured as "adverse event." Subject 070723001 in Cohort 4 was prematurely withdrawn from the study because she was randomized before the protocol amendment; enrollment into this cohort was approved at the site (she did not receive any study drug and, therefore, was categorized as "prematurely discontinued" from study drug treatment).

Abbreviations: CSR = clinical study report; ITT = intent-to-treat.

Source: CSR P903-23, Table 10.2-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.1.2.2.2-1.

Table of Demographic Characteristics

In both treatment groups, demographic characteristics were similar (**Table 38**). The majority of subjects were male, white, with a mean age of approximately 7 years (range 9 weeks - 17 years). The highest percentage enrollment was in Cohort 2 (children from 6 years to < 12 years) in both treatment arms.

Table 38 Demographic and Baseline Characteristics by Treatment Group Overall, Study P903-23—MITT Population.

Characteristic	*Ceftaroline (N = 107)*	*Comparator (N = 52)*
Age, years		
Mean (SD)	6.99 (5.10)	6.94 (5.25)
Median (range)	7.00 (0.2, 17.0)	6.00 (0.6, 17.0)
Age cohort, n (%)		
12 years to < 18 years (Cohort 1)	23 (21.5)	13 (25.0)
6 years to < 12 years (Cohort 2)	36 (33.6)	15 (28.8)
24 months to < 6 years (Cohort 3)	23 (21.5)	12 (23.1)
2 months to < 24 months (Cohort 4)	25 (23.4)	12 (23.1)
Sex, n (%)		
Male	57 (53.3)	31 (59.6)
Female	50 (46.7)	21 (40.4)
Race, n (%)		
White	91 (85.0)	48 (92.3)
Black or African American	15 (14.0)	4 (7.7)
Other	1 (0.9)	0
Ethnicity, n (%)		
Hispanic or Latino	23 (21.5)	15 (28.8)
Non-Hispanic or Latino	84 (78.5)	37 (71.2)
Weight, kg		
Mean (SD)	30.06 (21.07)	30.95 (21.50)
Median (range)	22.00 (4.7, 98.8)	22.00 (8.4, 83.0)

Characteristic	*Ceftaroline (N = 107)*	*Comparator (N = 52)*
Height, cm		
Mean (SD)	119.67 (35.10)	123.34 (36.09)
Median (range)	120.50 (52.0, 187.9)	119.60 (60.0, 186.1)
n	106	52
Creatinine clearance, mL/min/1.73 m^2		
Mean ± SD	119.19 (33.57)	119.74 (36.58)
Median (range)	113.05 (44.7, 305.6)	105.60 (58.2, 222.4)
n	106	51
Creatinine clearance category, n (%)		
≥ 80 mL/min/1.73 m^2	99 (92.5)	45 (86.5)
≥ 50 to < 80 mL/min/1.73 m^2	6 (5.6)	6 (11.5)
< 50 mL/min/1.73 m^2	1 (0.9)	0

Abbreviations: CSR = clinical study report; MITT = modified intent-to-treat; SD = standard deviation.
Source: CSR P903-23, Table 11.2.1-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.1.2.2.2-1.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Approximately two-thirds of subjects had cellulitis or erysipelas and approximately one-quarter had major abscesses. The most common locations of the primary infection sites included the legs, buttocks, and head, and were similar between the ceftaroline and comparator groups.

Approximately 30% of pediatric subjects had a therapeutic procedure performed at the primary infection site prior to study randomization. The types of procedures performed were similar between the two treatment groups. In addition, 15% and 12% of subjects in the ceftaroline and comparator groups, respectively, required significant surgical intervention within 48 hours prior to randomization.

The percentage of subjects in the ceftaroline and comparator groups who received prior systemic antibacterials within 96 hours before the first dose of IV study drug was similar in both treatment arms (66.4% [77/107] and 67.3% [35/52], respectively).

Although specimens or blood samples were obtained from almost all of the subjects enrolled in study P903-23, a significant percentage of subjects had no isolates obtained or no pathogen identified. Of the isolates, Gram-positive organisms were the most frequent in both treatment arms, with *S. aureus* the most common pathogen identified.

Concomitant antibacterial medications received from randomization through late follow-up for the MITT Population of Study P903-23 were similar in both the ceftaroline fosamil and comparator arms (16.8% [18/107] versus 17.3% [9/52], respectively).

Table 39 Clinical Outcomes at Test-of-Cure by Treatment Group Overall, Study P903-23—MITT and mMITT Populations.

Outcome	*Ceftaroline (N = 107) n (%)*	*Comparator (N = 52) n (%)*	*Difference*
MITT Population			
N			
Clinical cure	101 (94.4)	45 (86.5)	7.9%
95% CI	(88.2, 97.9)	(74.2, 94.4)	(–1.2, 20.2)
Clinical failure	0	1 (1.9)	—
Observed failure at EOIV	0	1 (1.9)	—
Observed failure at EOT	0	0	—
Observed failure at TOC	0	0	—
Indeterminate	6 (5.6)	6 (11.5)	—
mMITT Population			
N	52	22	—
Clinical cure	49 (94.2)	18 (81.8)	12.4%
95% CI	(84.1, 98.8)	(59.7, 94.8)	(–2.1, 33.6)
Clinical failure	0	0	—
Observed failure at EOIV	0	0	—
Observed failure at EOT	0	0	—
Observed failure at TOC	0	0	—
Indeterminate	3 (5.8)	4 (18.2)	—

Notes: Difference is the ceftaroline treatment group percentage minus comparator group percentage; the CIs for individual groups are calculated using the exact Clopper-Pearson method; the CIs for the difference between treatment groups are calculated using the method of Miettinen and Nurminen without stratification.
The symbol "—" signifies that data are not applicable.
Abbreviations: CI = confidence interval; EOIV = End-of-Intravenous Study Drug; EOT = End-of-Therapy; MITT = Modified Intent-to-Treat; mMITT = Microbiological Modified Intent-to-Treat; TOC = Test-of-Cure.
Source: ABSSSI Module 2.7.3, Table 6.2.3.1-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.2.3.1-1.

Reviewer comment: *Clinical cure rates at TOC in the pediatric studies are similar to that observed in the adult studies (**Table 40**).*

Table 40 Clinical Response at Test-of-Cure, Pooled Adult Studies P903-06 and P903-07—MITT and mMITT Populations.

Population/Clinical Response	*Pooled Phase 3 Studies (06, 07)*	
	Ceftaroline n (%)	*Vancomycin plus Aztreonam n (%)*
MITT		
N	693	685
Clinical Cure	595 (85.9)	586 (85.5)
Clinical Failure	54 (7.8)	49 (7.2)
Indeterminate	44 (6.3)	50 (7.3)
Crude Difference (95% CI)	0.3	—
Weighted Difference (95% CI)	0.3 (–3.4, 4.0)	—
mMITT		
N	540	522
Clinical Cure	469 (86.9)	453 (86.8)
Clinical Failure	38 (7.0)	28 (5.4)
Indeterminate	33 (6.1)	41 (7.9)
Crude Difference (95% CI)	0.1	—
Weighted Difference (95% CI)	0.1 (–4.0, 4.2)	—

Notes: Crude Difference = Difference in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Weighted Difference = Weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Confidence intervals are calculated using Miettinen and Nurminen method stratified by study.
The symbol "—" signifies that data are not applicable.
Abbreviations: CI = confidence interval; cSSSI = complicated skin and skin structure infection; MITT = modified intent-to-treat; mMITT = microbiological modified intent-to-treat; NDA = New Drug Application.
Source: Module 2.7.3-cSSSI, Tables 3.2.1–1 and 3.2.2.1–1 in the original NDA (Sequence 0000).

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.2.3.2-1.

Table 41 Clinical Outcomes at LFU by Treatment Group Overall, Study P903-23— MITT Population.

Outcome	*Ceftaroline (N = 107)*	*Comparator (N = 52)*	*Difference (%)*
Clinical cure at TOC[a], n	101	45	—
Sustained clinical cure, n (%)	99 (98.0)	45 (100.0)	–2.0
95% CI	(93.0, 99.8)	(92.1, 100.0)	(–7.0, 6.0)
Clinical relapse, n (%)	0	0	—
Indeterminate, n (%)	2 (2.0)	0	—

Notes: Difference is the ceftaroline treatment group percentage minus comparator group percentage; the CIs for individual groups are calculated using the exact Clopper-Pearson method; the CIs for the difference between treatment groups are calculated using the method of Miettinen and Nurminen without stratification.

The symbol "—" signifies that data are not applicable.

a Percentages are based on the number of subjects assessed as clinical cure at TOC.

Abbreviations: CI = confidence interval; CSR = clinical study report; LFU = Late Follow-up; MITT = modified intent-to-treat; TOC = Test-of-Cure.

Source: CSR P903-23, Table 11.4.1.2-4.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – ABSSSI, Table 6.2.4.1-1.

13.6. Additional Study Design Information for Study P903-31

Table 42 Study P903-31 Schedule of Assessments and Procedures

	Assessment or Procedure	*Baseline*[1]	*Treatment*					*Follow-up*	
			SD 1[2] *Postdose*	*SDs 2 and 3*	*SDs 4 to ≤ 14*[3]	*EOIV*[4]	*EOT*[5] *(oral only)*	*TOC*[6]	*LFU*[7]
	ICF (and assent form, if applicable)[8]	X							
	Verify inclusion/exclusion criteria	X							
Clinical	Medical and surgical history	X							
	Complete physical examination	X							
	Prior and concomitant medications	X	X	X	X	X	X	X	X
	Height (length) and weight	X				X[9]	X[9]	X[9]	
	Vital signs and oxygen saturation	X	X	X	X	X	X	X	X[10]
	Record adjunctive therapeutic procedures (if performed)		X	X	X	X	X	X	X
	Pain scale[11]	X	X	X	X	X	X	X	X[10]
	Symptom questionnaire[12]	X	X	X	X[13]	X	X	X	X[10]
	CABP physical findings[14]	X	X	X	X	X	X	X	X[10]
	CXR or CT scan[15]	X	if clinically indicated						
	Clinical outcome					X[16]	X[16]	X[16]	X[17]
	AEs and SAEs[18]	X	X	X	X	X	X	X	X
Laboratory	CBC with differential, chemistry panel[19]	X			X[20]	X[21]		X[22]	
	CRP (with chemistry panel)	X	X[23]			X[21]			
	Direct Coombs test	X						X	
	Urine pregnancy test[24]	X						X	
	CrCl calculation	X	if clinically indicated						
Micro	Respiratory sample[25]	X	if clinically indicated						
	Nasopharyngeal swab for diagnostic viral testing[26]	X							
	Blood sample for culture	X	if clinically indicated[27]						
	Blood sample for serology testing for atypical pathogens[28]	X							
	Urine sample for *S. pneumoniae* antigen test[29]	X							
PK	Blood for PK analyses[30]			X					
	Standard of care CSF and matching PK blood samples[30]		X						
	Randomization[31]	X							
	Study drug administration		X	X	X[32]	X	X		

Abbreviations: AE = adverse event; CABP = community-acquired bacterial pneumonia; CBC = complete blood count; CRP = C-reactive protein; CSF = cerebrospinal fluid; CrCl = creatinine clearance; CT = computed tomography; CXR = chest radiograph; EOIV = End-of-Intravenous Study Drug; EOT = End-of-Therapy; ICF = informed consent form; IV = intravenous; LFU = Late Follow-up; PK = pharmacokinetic; SAE = serious adverse event; SD = Study Day; TOC = Test-of-Cure.

1 Baseline assessments were to be conducted within 24 hours before first dose of IV study drug.

2 SD 1 was the first day of IV study drug administration; subsequent study days were consecutive calendar days. SD 1 assessments were to be conducted after administration of at least 1 dose of IV study drug.

3 On SDs 4 to ≤ 14, study drug administration applied to all subjects and daily assessments were to be conducted only for subjects on IV study drug.

4 EOIV assessments were to be conducted in person within 24 hours after administration of the last dose of IV study drug or at time of premature discontinuation of study drug or early withdrawal from study (if on IV study drug). The EOIV assessments were conducted in place of the regular study visit (eg, SDs 4 to ≤ 14) assessments that would have been performed the day of that visit. A subject may have been eligible to switch to oral study drug on or after SD 4 (Section 9.2.1); EOIV assessments occurred before starting oral study drug.

5 EOT assessments were to be conducted in person within 48 hours after the last dose of oral study drug or at time of premature discontinuation of study drug or early withdrawal from study (if on oral study drug).

6 TOC assessments were to be conducted in person 8 to 15 days after last dose of any study drug (IV or oral).

7 LFU assessments were to be conducted 21 to 35 days after last dose of any study drug (IV or oral). LFU was conducted by telephone for any subject who had not experienced clinical relapse, had no ongoing AEs or SAEs at TOC, or had not developed AEs or SAEs since TOC. The subject was immediately scheduled for an in-person visit if symptoms of relapse or new AEs or SAEs were noted, or at the discretion of the Blinded Observer or Investigator.

8 Informed consent was to be obtained from parent(s) (or other legally acceptable representative[s]) in writing and informed assent from subject (if age appropriate according to local requirements) before any study assessments or procedures were initiated.

9 Recorded weight only.

10 Was not performed if LFU was conducted via telephone.

11 Blinded Observer: Use age-appropriate scale.

12 Blinded Observer.

13 Was to be conducted daily while subject was on IV study drug.

14 Blinded Observer: Was to evaluate physical findings of CABP.

15 According to procedures outlined in the protocol.

16 Blinded Observer: Was to assess clinical outcome per Table 9.5.2.2.4–1, Table 9.5.2.2.4–2, and Table 9.5.2.2.4–3.

17 Blinded Observer: Was to assess subjects for clinical relapse per Table 9.5.2.2.4–4.

18 Blinded Observer and Investigator: Collected AEs and SAEs from signing of the ICF (and assent form if applicable) until at least 30 days after any dose of study drug (IV or oral) (or LFU, whichever was later); study center staff were to follow unresolved AEs and SAEs at LFU until resolution or stabilization.

19 Refer to Section 9.5.4.4 for the list of laboratory tests. Local safety laboratory tests were to be conducted at additional time points as clinically indicated.

20 Was to be conducted on Study Day 7 if subject was still on IV study drug at that time.

21 If EOIV occurred within 48 hours after these assessments were to be performed on Study Day 7, these assessments were not repeated.

22 Was to be conducted at TOC only if subject had an abnormal (high/low flag) result on or after EOIV.

23 If a subject was on IV study drug and blood was drawn for a standard of care chemistry panel, a test for CRP was to be included.

24 Test was to be conducted if subject was a female who had reached menarche. If a pregnancy test was positive postbaseline, reporting requirements were to be followed as outlined in Section 9.5.4.3.

25 At baseline (preferably before any antibiotics were administered), every attempt was to be made to obtain respiratory samples; postbaseline, repeat respiratory samples were attempted, if clinically indicated.

26 At baseline (± 24 hours), every attempt was to be made to obtain a nasopharyngeal swab specimen.

27 If clinically indicated and not already collected per standard of care, blood for culture was to be obtained; repeat blood cultures upon knowledge of a positive result from any test until sterilization were to be confirmed.

28 Blood samples for serology testing of atypical pathogens per study-specific procedures outlined in the microbiology and clinical laboratory manual were to be obtained.

29 If clinically possible, every attempt was to be made to obtain a urine sample for the *Streptococcus pneumoniae* antigen test at baseline or any time on Study Day 1 per study-specific procedures outlined in the microbiology and clinical laboratory manual.

30 PK and CSF samples were to be collected per instructions in Section 9.5.3 and as outlined in the PK Sample Handling and Shipping Manual.

31 Verification that the subject met all study inclusion, and no exclusion criteria, was to be made before randomization.

32 Administered study drug.

Source: NDA 200327 Clinical Study Report for P903-31, Table 9.5.1-1, Schedule of Assessments and Procedures.

13.7. Clinical and Microbiologic Outcome Definitions – Study P903-31 and P903-24

Table 43 Study P903-31 Clinical Outcomes Categories at the End-of-Intravenous Study Drug

Outcome	*Definition*
Clinical Cure	Resolution of all acute signs and symptoms of CABP or improvement to such an extent that no further antimicrobial therapy was required
Clinical Improvement	Subjects who switched to oral study drug and met all of the following criteria at EOIV: • Afebrile (temperature ≤ 38.0°C) for at least 24 hours • No new and improvement in at least 1 symptom (ie, cough, dyspnea, sputum production, chest pain) from baseline and worsening of none
Clinical Failure[a]	Subjects who met **any** of the following: • Discontinuation of study drug due to insufficient therapeutic effect, which included persistence, incomplete clinical resolution, or worsening in signs and symptoms of CABP that required alternative nonstudy antimicrobial therapy • Discontinuation of study drug due to an AE and subject required an alternative nonstudy antimicrobial therapy for CABP • Death in which CABP was contributory
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which CABP was clearly noncontributory • Lost to follow-up • Extenuating circumstances that precluded classification as a cure, ***improvement,*** or failure

Abbreviations: AE = adverse event; CABP = community-acquired bacterial pneumonia; EOIV = End-of-Intravenous Study Drug; EOT = End-of-Therapy; TOC = Test-of-Cure.

a A clinical failure at EOIV was to be carried forward to EOT and TOC.

Source: NDA 200327 Clinical Study Report for P903-31, Table 9.5.2.2.4-1, Clinical Outcomes Categories at the End-of-Intravenous Study Drug.

Table 44 Study P903-31 Clinical Outcomes Categories at the End-of-Therapy

Outcome	*Definition*
Clinical Cure	Resolution of all acute signs and symptoms of CABP or improvement to such an extent that no further antimicrobial therapy was required
Clinical Failure[a]	Subjects who met any of the following: • Discontinuation of study drug due to insufficient therapeutic effect, which included persistence, incomplete clinical resolution, or worsening in signs and symptoms of CABP that required alternative nonstudy antimicrobial therapy • Discontinuation of study drug due to an AE and subject required an alternative nonstudy antimicrobial therapy for CABP • Death in which CABP was contributory
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which CABP was clearly noncontributory • Lost to follow-up • Extenuating circumstances that precluded classification as a cure or failure

Abbreviations: AE = adverse event; CABP = community-acquired bacterial pneumonia; EOT = End-of-Therapy; TOC = Test-of-Cure.

a A clinical failure at EOT was to be carried forward to TOC.

Source: NDA 200327 Clinical Study Report for P903-31, Table 9.5.2.2.4-2, Clinical Outcomes Categories at the End-of-Therapy.

Table 45 Study P903-31 Clinical Outcomes Categories at Test-of-Cure

Outcome	*Definition*
Clinical Cure	Resolution of all acute signs and symptoms of CABP or improvement to such an extent that no further antimicrobial therapy was required
Clinical Failure	Subjects who met either of the following criteria: • Incomplete resolution or worsening of CABP signs or symptoms or development of new signs or symptoms which required an alternative nonstudy antimicrobial therapy • Death in which CABP was contributory
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which CABP was clearly noncontributory • Lost to follow-up • Extenuating circumstances that precluded classification as a cure or failure

Abbreviations: CABP = community-acquired bacterial pneumonia

Source: NDA 200327 Clinical Study Report for P903-31, Table 9.5.2.2.4-3, Clinical Outcomes Categories at Test-of-Cure.

Table 46 Study P903-31 Clinical Outcomes Categories at Late Follow-up

Outcome	*Definition*
Sustained Clinical Cure	Continued favorable response, defined as resolution of all acute signs and symptoms of CABP and no further antimicrobial therapy was required
Clinical Relapse	Subjects who met either of the following criteria: • Reappearance or worsening of signs and symptoms of CABP that required further antimicrobial therapy • Death after TOC in which CABP was contributory
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Death in which CABP was clearly noncontributory • Lost to follow-up • Extenuating circumstances that precluded classification as sustained clinical cure or clinical relapse

Abbreviations: CABP = community-acquired bacterial pneumonia; LFU = Late Follow-up; TOC = Test-of-Cure.
Note: Clinical outcome at LFU was only to be assessed in subjects who were considered clinically cured at TOC.

Source: NDA 200327 Clinical Study Report for P903-31, Table 9.5.2.2.4-4, Clinical Outcomes Categories at Late Follow-up.

Microbiologic outcomes categories at Test-of-Cure are summarized in .

Table 47 Study P903-31 Microbiologic Outcomes Categories at Test-of-Cure

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

Abbreviation: TOC = Test-of-Cure.
a For subjects who were clinical failures before TOC, the microbiological outcome was to be carried forward to TOC and was to be determined based on the cultures and/or clinical outcome at the time of the early clinical failure determination.

Source: NDA 200327 Clinical Study Report for P903-31, Table 9.5.2.3.1-1, Microbiologic Outcomes Categories at Test-of-Cure.

Emergent infections were defined as organisms or pathogens first appearing after baseline. Categories for emergent infections are summarized in .

Table 48 Study P903-31 Categories for Emergent Infections

Infection Category	*Definition*
Colonization	Isolation of new organism(s) not present at baseline from the site of infection in a subject who was assessed as a clinical cure
Superinfection	Isolation of new pathogen(s) not present at baseline from the site of infection during treatment with any study drug (IV or oral), which was associated with emergence or worsening of signs and symptoms of CABP
New infection	Isolation of new pathogen(s) not present at baseline from the site of infection after completion of all study drug therapy (IV and oral), which was associated with emergence or worsening of signs and symptoms of CABP

Abbreviations: CABP = community-acquired bacterial pneumonia; IV = intravenous.

Source: NDA 200327 Clinical Study Report for P903-23, Table 9.5.2.3.2-1, Emergent Infections.

13.8. Additional Study Design Information for Study P903-24

Table 49 Study P903-31 Schedule of Assessments and Procedures

	Assessment or Procedure	*Baseline*[1]	*Treatment*					*Follow-up*	
			SD 1[2] *Postdose*	*SDs 2 and 3*	*SDs 4 to ≤ 21*[3]	*EOIV*[4]	*EOT*[5] *(oral only)*	*TOC*[6]	*LFU*[7]
	ICF (and assent form, if applicable)[8]	X							
	Verify inclusion/exclusion criteria	X							
Clinical	Medical and surgical history	X							
Clinical	Complete physical examination	X							
Clinical	Prior and concomitant medications	X	X	X	X	X	X	X	X
Clinical	Height (length) and weight	X				X[9]	X[9]	X[9]	
Clinical	Vital signs including oxygen saturation	X	X	X	X	X	X	X	X[10]
Clinical	Record adjunctive therapeutic procedures (if performed)		X	X	X	X	X	X	X
Clinical	Pain scale[11]	X	X	X	X	X	X	X	X[10]
Clinical	Symptom questionnaire[12]	X	X	X	X[13]	X	X	X	X[10]
Clinical	CABP physical findings[14]	X	X	X	X	X	X	X	X[10]
Clinical	CXR or CT scan[15]	X	if clinically indicated						
Clinical	Clinical outcome					X[16]	X[16]	X[16]	X[17]
Clinical	AEs and SAEs[18]	X	X	X	X	X	X	X	X
Laboratory	CBC with differential, chemistry panel[19]	X			X[20]	X[21]		X[22]	
Laboratory	CRP (with chemistry panel)	X		X[23]		X[21]			
Laboratory	Direct Coombs' test	X						X	
Laboratory	Urine pregnancy test[24]	X						X	
Laboratory	CrCl calculation	X	if clinically indicated						

	Assessment or Procedure	*Baseline*[1]	*Treatment*					*Follow-up*	
			SD 1[2] *Postdose*	*SDs 2 and 3*	*SDs 4 to ≤ 21*[3]	*EOIV*[4]	*EOT*[5] *(oral only)*	*TOC*[6]	*LFU*[7]
Microbiology	Respiratory sample[25]	X	if clinically indicated						
	Nasopharyngeal swab for diagnostic viral testing[26]	X							
	Blood sample for culture	X	if clinically indicated[27]						
	Blood sample for serology testing for atypical pathogens[28]	X						X	
	Urine sample for *S. pneumoniae* antigen test[29]	X							
PK	Blood for PK analyses[30]			X					
	Standard of care CSF and matching PK blood samples[30]		X						
	Randomization[31]	X							
	Study drug administration		X	X	X[32]	X	X		

Abbreviations: AE = adverse event; CABP = community-acquired bacterial pneumonia; CBC = complete blood count; CrCl = creatinine clearance; CRP = C-reactive protein; CSF = cerebrospinal fluid; CT = computed tomography; CXR = chest radiograph; EOIV = End-of-Intravenous Study Drug; EOT = End-of-Therapy; ICF = informed consent form; IV = intravenous; LFU = Late Follow-up; PK = pharmacokinetic; SAE = serious adverse event; SD = Study Day; TOC = Test-of-Cure.

1 Baseline assessments were to be conducted within 24 hours before first dose of IV study drug.
2 SD 1 was the first day of IV study drug administration; subsequent study days were consecutive calendar days. SD 1 assessments were to be conducted after administration of at least 1 dose of IV study drug.
3 On SDs 4 to ≤ 21, study drug administration was to apply to all subjects and daily assessments were to be conducted only for subjects on IV study drug.
4 EOIV assessments were to be conducted in person within 24 hours after administration of the last dose of IV study drug or at time of premature discontinuation of study drug or early withdrawal from study (if on IV study drug). The EOIV assessments were to be conducted in place of the regular study visit (eg, SDs 4 to ≤ 21), assessments that would have been performed the day of that visit. The EOIV assessments were to have occurred before starting oral study drug (Section 9.4.2.1), if applicable.
5 EOT assessments were to be conducted in person within 48 hours after the last dose of oral study drug or at time of premature discontinuation of study drug or early withdrawal from study (if on oral study drug).
6 TOC assessments were to be conducted in person 8 to 15 days after last dose of any study drug (IV or oral).
7 LFU assessments were to be conducted 21 to 35 days after last dose of any study drug (IV or oral). The LFU was to be conducted via telephone for any subject who had not experienced clinical relapse, did not have ongoing AEs or SAEs at TOC, or did not develop AEs or SAEs since TOC. If symptoms of relapse or new AEs or SAEs were noted, or at the discretion of the Blinded Observer or Investigator, the subject was to be immediately scheduled for an in-person visit.

8 Informed consent was to be obtained from parent(s) (or other legally acceptable representative[s]) in writing and informed assent from subject (if age appropriate according to local requirements) before initiating any study assessments or procedures.
9 Weight to be recorded only.
10 Was not to be performed if LFU was conducted via telephone.
11 Blinded Observer: Used age-appropriate scale (Section 9.5.5.1).
12 Blinded Observer: Symptom questionnaire provided in Protocol (Appendix 6.1.1).
13 Was to be conducted daily while subject was on IV study drug.
14 Blinded Observer: Was to evaluate physical findings of CABP.
15 According to procedures outlined in Appendix II of the Protocol.
16 Blinded Observer: Clinical outcome was to be assessed per Table 9.5.2.2.4–1, Table 9.5.2.2.4–2, and Table 9.5.2.2.4–3.
17 Blinded Observer: Subjects considered clinically cured at TOC were to be assessed for clinical relapse per Table 9.5.2.2.4–4.
18 Blinded Observer and Investigator: AEs and SAEs were to be collected from signing of the ICF (and assent form if applicable) until at least 30 days after any dose of study drug (IV or oral) (or LFU, whichever was later); study center staff were to follow unresolved AEs and SAEs at LFU until resolution or stabilization.
19 Refer to Section 9.5.4.4 for the list of laboratory tests. Local safety laboratory tests were to be conducted at additional time points as clinically indicated.
20 To be conducted on Study Day 7 if subject was still on IV study drug at that time.
21 If EOIV occurred within 48 hours after these assessments were performed on Study Day 7, the assessments were not to be repeated.
22 To be conducted at TOC only if subject had an abnormal (high/low flag) result on or after EOIV.
23 If a subject was on IV study drug and blood was drawn for a standard of care chemistry panel, a test for CRP was to be included.
24 Test was to be conducted if subject was a female who had reached menarche. If a pregnancy test was positive postbaseline, reporting requirements were to be followed per Section 9.5.4.3.
25 At baseline (preferably before any antibiotics were administered), every attempt was to be made to obtain respiratory samples; postbaseline; repeat respiratory samples were to be attempted if clinically indicated.
26 At baseline (± 24 hours), every attempt was to be made to obtain a nasopharyngeal swab specimen.
27 If clinically indicated, and not already collected per standard of care, blood was to be obtained for culture; blood cultures were to be repeated upon knowledge of a positive result from any visit until sterilization was confirmed.
28 Blood samples for serology testing of atypical pathogens per study-specific procedures outlined in the microbiology and clinical laboratory manual were to be obtained.
29 If clinically possible, every attempt was to be made to obtain a urine sample for the *Streptococcus pneumoniae* antigen test at baseline or any time on Study Day 1 per study-specific procedures outlined in the microbiology and clinical laboratory manual.
30 PK and CSF samples were to be collected per instructions in Section 9.5.3 and as outlined in the PK Sample Handling and Shipping Manual.
31 Verification that the subject met all study inclusion and no exclusion criteria before randomization.
32 Administration of study drug.

Source: NDA 200327 Clinical Study Report for P903-24, Table 9.5.1-1, Schedule of Assessments and Procedures.

13.9. Additional Results – Study P903-31 and Study P903-24

Patient Disposition

The number and percentage of subjects in each analysis population, as well as the reasons for exclusion from the respective populations by treatment group in the pediatric CABP studies, are shown in .

The percentage of subjects in all of the populations was similar between the ceftaroline and the ceftriaxone treatment groups in Study P903-31. Isolation of a sole atypical pathogen was the most common reason for exclusion from the MITT Population in both treatment groups.

In Study P903-24, two subjects, 1 in each treatment group, were excluded from the MITT Population because of the presence of a sole atypical pathogen.

Table 50 Subject Populations and Reasons for Exclusions, Studies P903 31 and P903 24— ITT Population.

Study Populations Reasons for Exclusion	*P903-31*		*P903-24*	
	Ceftaroline (N = 122) n (%)	*Ceftriaxone (N = 39) n (%)*	*Ceftaroline (N = 30) n (%)*	*Comparator (N = 10) n (%)*
ITT Population	**122 (100.0)**	**39 (100.0)**	**30 (100.0)**	**10 (100.0)**
MITT Population	**107 (87.7)**	**36 (92.3)**	**29 (96.7)**	**9 (90.0)**
No study drug taken	1 (0.8)	0	0	0
No confirmed CABP[a]	1 (0.8)	0	0	0
Sole atypical pathogen	14 (11.5)	3 (7.7)	1 (3.3)	1 (10.0)
mMITT Population	**24 (19.7)**	**9 (23.1)**	**15 (50.0)**	**3 (30.0)**
Not in MITT Population	15 (12.3)	3 (7.7)	1 (3.3)	1 (10.0)
No typical pathogen identified at baseline	98 (80.3)	30 (76.9)	15 (50.0)	7 (70.0)
CE Population	**98 (80.3)**	**36 (92.3)**	**26 (86.7)**	**9 (90.0)**
Not in MITT Population	15 (12.3)	3 (7.7)	1 (3.3)	1 (10.0)
Received < 80% of study drug	0	0	1 (3.3)	0
Less than the minimum number of days of IV or oral study drug	0	0	0	0
Test-of-Cure visit out of window	10 (8.2)	1 (2.6)	1 (3.3)	0
Concomitant antimicrobial violation	2 (1.6)	0	1 (3.3)	0
Received incorrect study drug	0	0	0	0
Unblinded prior to database lock	0	0	0	0
Additional inclusion/exclusion criteria violation[b]	3 (2.5)	0	0	0
ME Population	**23 (18.9)**	**9 (23.1)**	**13 (43.3)**	**3 (30.0)**
Not in mMITT Population	98 (80.3)	30 (76.9)	15 (50.0)	7 (70.0)
Not in CE Population	24 (19.7)	3 (7.7)	4 (13.3)	1 (10.0)

Note: Reasons for exclusion from study populations are not mutually exclusive and subjects may be counted in multiple categories.

a Confirmed CABP was defined as meeting inclusion criteria #3 and component II (Study P903-31)/components II and III (Study P903-24) of inclusion criterion #4, and did not violate exclusion criteria #2, #3, and #4.

b Additional criteria included all components of inclusion criterion #4 and exclusion criterion #5.

Abbreviations: CABP = community-acquired bacterial pneumonia; CE = clinically evaluable; CSR = clinical study report; ITT = intent-to-treat; IV = intravenous; ME = microbiologically evaluable; MITT = modified intent-to-treat; mMITT = microbiological modified intent-to-treat.

Source: CSR P903-31, Table 10.1-1; CSR P903-24, Table 10.1-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.1.1-1.

The majority of subjects in Study P903-31 and P903-24 completed study drug therapy (). The percentage of subjects who discontinued IV or oral study drug was similar between treatment groups in Study P903-31. Sample sizes in Study P903-24 were too small to draw any conclusions.

Table 51 Study Drug Completion and Reasons for Premature Discontinuation of Study Drug, Studies P903-31 and P903-24—ITT Population.

Subject Status *Reason for Discontinuation*	*P903-31*		*P903-24*	
	Ceftaroline (N = 122) n (%)	*Ceftriaxone (N = 39) n (%)*	*Ceftaroline (N = 30) n (%)*	*Comparator (N = 10) n (%)*
Completed Study Drug	**111 (91.0)**	**35 (89.7)**	**27 (90.0)**	**10 (100.0)**
Premature discontinuation of any (IV or oral) study drug	**11 (9.0)**	**4 (10.3)**	**3 (10.0)**	**0**
Subject randomized, but did not receive study drug	1 (0.8)	0	0	0
Adverse event	2 (1.6)	0	2 (6.7)	0
Insufficient therapeutic effect	5 (4.1)	3 (7.7)	1 (3.3)	0
Withdrawal of consent	1 (0.8)	0	0	0
Other reasons[a]	2 (1.6)	1 (2.6)	0	0
Premature discontinuation of IV study drug	**9 (7.4)**	**4 (10.3)**	**3 (10.0)**	**0**
Subject randomized, but did not receive study drug	1 (0.8)	0	0	0
Adverse event	1 (0.8)	0	2 (6.7)	0
Insufficient therapeutic effect	5 (4.1)	3 (7.7)	1 (3.3)	0
Withdrawal of consent	1 (0.8)	0	0	0
Other reasons	1 (0.8)	1 (2.6)	0	0
Premature discontinuation of oral study drug	**2 (1.6)**	**0**	**0**	**0**
Adverse event	1 (0.8)	0	0	0
Other reasons	1 (0.8)	0	0	0

a In Study P903-31, 3 subjects discontinued IV or oral study drug due to other reasons: Subject 022931001, in the ceftriaxone group, discontinued IV study drug due to pneumonia caused by mycoplasma but completed the study; Subject 001131001 in the ceftaroline group discontinued oral study drug on day 3 at the discretion of the Investigator, and Subject 021931015, also in the ceftaroline group, discontinued IV study drug due to a change in diagnosis (ie, diagnosis of Kawasaki disease, which was also reported as an AE for this subject).

Abbreviations: CSR = clinical study report; ITT = intent-to-treat; IV = intravenous.

Source: CSR P903-31, Table 10.2-1; CSR P903-24, Table 10.2-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.1.2.2.1-1.

The majority of subjects in Study P903-31 completed the study and all subjects in Study P903-24 completed the study (). In Study P903-31, there was no discernible pattern regarding the reasons for premature withdrawal from the study.

Table 52 Subject Completion and Reasons for Premature Withdrawal from the Study, Studies P903-31 and P903-24—ITT Population.

Subject Status Reason for Discontinuation	*P903-31*		*P903-24*	
	Ceftaroline (N = 122) n (%)	*Ceftriaxone (N = 39) n (%)*	*Ceftaroline (N = 30) n (%)*	*Comparator (N = 10) n (%)*
Completed Study	**116 (95.1)**	**38 (97.4)**	**30 (100.0)**	**10 (100.0)**
Premature withdrawal from study	**6 (4.9)**	**1 (2.6)**	**0**	**0**
Subject did not meet inclusion/exclusion criteria	0	0	—	—
Withdrew consent	2 (1.6)	0	—	—
Lost to follow-up	1 (0.8)	1 (2.6)	—	—
Withdrawn by Sponsor or Investigator	0	0	—	—
Lack of compliance	0	0	—	—
Death	0	0	—	—
Other reasons[a]	3 (2.5)	0	—	—

Note: The symbol "—" signifies that data are not applicable.

a In Study P903-31, 3 subjects discontinued from the study due to other reasons: 2 of these subjects (Subject 001131001 and Subject 021931015) discontinued both study drug and the study due to other reasons as described in Table 6.1.2.2.1–1; however, the third subject (Subject 061231002) discontinued study drug due to a TEAE of headache, which also lead to withdrawal from the study; however, the reason for study withdrawal was reported as "other reasons."

Abbreviations: CSR = clinical study report; ITT = intent-to-treat.

Source: CSR P903-31, Table 10.2-1; CSR P903-24, Table 10.2-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.1.2.2.2-1.

Table of Demographic Characteristics

In both treatment groups for Study P903-31, demographic characteristics were similar (**Table 53**). The majority of subjects were male, white, with a mean age of approximately 4 years (range 10 weeks - 17 years). The highest percentage enrollment was in Cohort 3 (children from 24 months to < 6 years) in both treatment arms.

Similarly, in Study P903-24, the majority of subjects were male and white with a mean age of 5.4 years (range 16 weeks through 17 years). The highest percentage enrollment was also in Cohort 3 (ie, children from 24 months to < 6 years.

Table 53 Demographics and Baseline Characteristics, Studies P903-31 and P903-24— MITT Population.

Characteristic/Procedure	*P903-31*		*P903-24*	
	Ceftaroline (N = 107)	*Ceftriaxone (N = 36)*	*Ceftaroline (N = 29)*	*Comparator (N = 9)*
Age, years				
Mean ± SD	4.26 ± 3.45	3.98 ± 3.47	5.31 ± 4.65	5.74 ± 5.18
Median (range)	3.00 (0.2, 17.0)	3.00 (0.4, 16.0)	4.00 (0.3, 17.0)	4.00 (0.3, 16.0)
Age Cohort, n (%)				
12 years to < 18 years (Cohort 1)	7 (6.5)	2 (5.6)	4 (13.8)	2 (22.2)
6 years to < 12 years (Cohort 2)	19 (17.8)	7 (19.4)	7 (24.1)	1 (11.1)
24 months to < 6 years (Cohort 3)	58 (54.2)	21 (58.3)	12 (41.4)	4 (44.4)
2 months to < 24 months (Cohort 4)	23 (21.5)	6 (16.7)	6 (20.7)	2 (22.2)
Sex, n (%)				
Male	56 (52.3)	19 (52.8)	21 (72.4)	5 (55.6)
Female	51 (47.7)	17 (47.2)	8 (27.6)	4 (44.4)

Characteristic/Procedure	*P903-31*		*P903-24*	
	Ceftaroline (N = 107)	*Ceftriaxone (N = 36)*	*Ceftaroline (N = 29)*	*Comparator (N = 9)*
Race, n (%)				
White	105 (98.1)	35 (97.2)	27 (93.1)	8 (88.9)
Black or African American	1 (0.9)	0	1 (3.4)	1 (11.1)
Asian	1 (0.9)	1 (2.8)	0	0
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	0	0	1 (3.4)	0
Ethnicity, n (%)				
Hispanic or Latino	3 (2.8)	0	1 (3.4)	2 (22.2)
Non-Hispanic or Latino	104 (97.2)	36 (100.0)	28 (96.6)	7 (77.8)
Weight, kg				
Mean ± SD	20.01 ± 14.35	19.06 ± 12.94	25.87 ± 21.14	27.16 ± 26.12
Median (range)	16.0 (4.6, 100.0)	15.5 (6.9, 67.0)	19.2 (7.5, 94.8)	21.0 (6.9, 88.8)
Height, cm				
Mean ± SD	105.48 ± 24.73	105.02 ± 23.84	111.99 ± 32.90	111.28 ± 34.48
Median (range)	104.0 (52.0, 175.0)	101.0 (63.0, 164.0)	106.0 (59.0, 180.0)	101.0 (64.0, 169.0)
Creatinine clearance category, n (%)				
≥ 80 mL/min/1.73 m^2	84 (78.5)	23 (63.9)	24 (82.8)	9 (100.0)
≥ 50 to < 80 mL/min/1.73 m^2	23 (21.5)	13 (36.1)	5 (17.2)	0
< 50 mL/min/1.73 m^2	0	0	0	0

Abbreviations: CSR = clinical study report; MITT = modified intent-to-treat; SD = standard deviation.
Source: CSR P903-31, Table 11.2.1-1; CSR P903-24, Table 11.2.1-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.1.2.2.2-1.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

In Study P903-31, baseline pneumonia and disease characteristics were similar between the treatment groups (**Table 54**).

In Study P903-24, all subjects had radiologic findings consistent with a diagnosis of pneumonia with approximately one-half of the subjects in both treatment groups having pleural effusion, and approximately 60% of subjects having multi-lobar involvement.

Table 54 Pneumonia/Disease Characteristics and Radiographic Assessment at Baseline, Studies P903-31 and P903-24—MITT Population.

Characteristic	*P903-31*		*P903-24*	
	Ceftaroline (N = 107)	*Ceftriaxone (N = 36)*	*Ceftaroline (N = 29)*	*Comparator (N = 9)*
Nasopharyngeal swab for viral testing collected, n (%)[a]	106 (99.1)	36 (100.0)	28 (96.6)	9 (100.0)
All findings negative	31 (29.0)	11 (30.6)	6 (20.7)	3 (33.3)
One or more findings positive	73 (68.2)	25 (69.4)	22 (75.9)	6 (66.7)
History of pneumococcal vaccination, n (%)	54 (50.5)	18 (50.0)	5 (17.2)	2 (22.2)
C-reactive protein (mg/dL)				
Mean ± SD	11.118 ± 12.880	12.430 ± 12.503	20.312 (15.787)	16.080 (12.499)
Median (range)	5.400 (0.00, 57.30)	9.634 (0.00, 50.33)	19.66 (0.60, 48.00)	15.90 (3.26, 31.57)
Chest x-ray completed, n (%)	107 (100.0)	36 (100.0)	24 (82.8)	7 (77.8)
CT scan completed	0	0	2 (6.9)	0
Both chest x-ray and CT scan	0	0	3 (10.3)	2 (22.2)
Pleural effusion present, n (%)				
Unilateral	12 (11.2)	10 (27.8)	11 (37.9)	4 (44.4)
Right side	7 (6.5)	3 (8.3)	10 (34.5)	2 (22.2)
Left side	5 (4.7)	7 (19.4)	1 (3.4)	2 (22.2)
Bilateral	0	1 (2.8)	3 (10.3)	1 (11.1)
Lobes involved, n (%)				
None	0	0	0	0
One lobe	75 (70.1)	22 (61.1)	12 (41.4)	4 (44.4)
Multiple lobes	32 (29.9)	14 (38.9)	17 (58.6)	5 (55.6)

a Subjects with a nasopharyngeal swab collected and no positive findings but 1 or more indeterminate findings were not included in either subcategory.

Abbreviations: CSR = clinical study report; MITT = modified intent-to-treat; SD = standard deviation.

Source: CSR P903-31, Table 11.2.2-1; CSR P903-24, Table 11.2.2-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.1.3.2.1-1.

In Study P903-31, respiratory specimens for microbiological testing were obtained from approximately 8% of subjects in both treatment groups at baseline.

***Reviewer comment**: The low recovery of a bacterial respiratory specimen at baseline is typical for the pediatric population.*[15]

In Study P903-24, respiratory samples were obtained from 37.9% of subjects in the ceftaroline group and 66.7% of subjects in the comparator group. In 13.8% of subjects in the ceftaroline group, *S. aureus* was identified as a pathogen (including 1 subject with an isolate of MRSA) compared to 1 subject (11.1%) in the comparator group (MSSA isolate).

In Study P903-31, concomitant antibacterial medications received within 96 hours before the first dose of IV study drug were similar in both the ceftaroline fosamil and comparator arms (43.9% [47/107] versus 47.2% [17/36], respectively).

In Study P903-24, In Study P903-24, more than half of the subjects in both treatment groups (62.1% [18/29] in the ceftaroline group and 55.6% [5/9] in the comparator group) received prior systemic antibacterial medications within 96 hours before the first dose of IV study drug.

Similar to the pediatric studies, in the MITTE Population of the pooled Phase 3 adult CABP studies, 40.9% of subjects in the ceftaroline group and 45.4% of subjects in the ceftriaxone group had previous antibiotic usage.

Table 55 Clinical Outcomes at End-of-Intravenous Study Drug, End-of-Therapy, and Test-of-Cure Visits, Studies P903-31 and P903-24—MITT and mMITT Populations.

Outcome	*P903-31*			*P903-24*		
	Ceftaroline n (%)	*Ceftriaxone n (%)*	*Difference (%)*	*Ceftaroline n (%)*	*Comparator n (%)*	*Difference (%)*
MITT Population						
N	107	36	—	29	9	—
Clinical cure	94 (87.9)	32 (88.9)	–1.0	26 (89.7)	9 (100.0)	–10.3
95% CI	(80.1, 93.4)	(73.9, 96.9)	(–11.5, 14.1)	—	—	(–26.7, 21.0)
Clinical failure	8 (7.5)	4 (11.1)	—	3 (10.3)	0	—
At EOIV	7 (7.5)	3 (8.3)	—	3 (10.3)	0	—
At EOT	0	1 (2.8)	—	0	0	—
At TOC	1 (0.9)	0	—	0	0	—
Indeterminate	5 (4.7)	0	—	0	0	—
mMITT Population						
N	24	9	—	15	3	—
Clinical cure	19 (79.2)	7 (77.8)	1.4	13 (86.7)	3 (100.0)	–13.3
95% CI	(57.8, 92.9)	(40.0, 97.2)	(–25.7, 37.6)	—	—	(–38.7, 46.5)
Clinical failure	4 (16.7)	2 (22.2)	—	2 (13.3)	0	—
At EOIV	3 (12.5)	1 (11.1)	—	2 (13.3)	0	—
At EOT	0	1 (11.1)	—	0	0	—
At TOC	1 (4.2)	0	—	0	0	—
Indeterminate	1 (4.2)	0	—	0	0	—

Notes: Difference is the ceftaroline treatment group percentage minus the ceftriaxone group percentage; the CIs for individual groups are calculated using the exact Clopper-Pearson method; the CIs for the difference between treatment groups were calculated using the method of Miettinen and Nurminen without stratification.
The symbol "—" signifies that data are not applicable.
Abbreviations: MITT = Modified Intent-to-Treat; mMITT = microbiological Modified Intent-to-Treat; EOIV = End-of-Intravenous Study Drug; EOT = End-of-Therapy; TOC = Test-of-Cure; CI = confidence interval.
Source: CABP Module 2.7.3, Table 6.2.3.1-1.

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.2.3.1-1.

Table 56 Clinical Response at Test-of-Cure, Pooled Phase 3 Adult Studies—MITTE and mMITTE Populations.

Population/Clinical Response	*Pooled Phase 3 Studies (08, 09)*	
	Ceftaroline n (%)	*Ceftriaxone n (%)*
MITTE		
N	580	573
Clinical Cure	479 (82.6)	439 (76.6)
Clinical Failure	81 (14.0)	114 (19.9)
Indeterminate	20 (3.4)	20 (3.5)
Crude Difference	6.0	—
Weighted Difference (95% CI)	6.0 (1.4, 10.7)	—
mMITTE		
N	165	168
Clinical Cure	138 (83.6)	126 (75.0)
Clinical Failure	23 (13.9)	37 (22.0)
Indeterminate	4 (2.4)	5 (3.0)
Crude Difference (95% CI)	8.6	—
Weighted Difference (95% CI)	8.7 (0.0, 17.4)	—

Notes: Crude Difference = Difference in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group).
Weighted Difference = Weighted Difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group).
Confidence intervals are calculated using Miettinen and Nurminen method stratified by study.
The symbol "—" signifies that data are not applicable.
Abbreviations: CABP = community-acquired bacterial pneumonia; CI = confidence interval; MITTE = modified intent-to-treat efficacy; mMITTE = microbiological modified intent-to-treat efficacy; NDA = New Drug Application.
Source: Module 2.7.3-CABP, Table 3.2.2-1 and Table 3.2.2-2 in the original NDA (Sequence 0000).

Source: NDA 200327 Module 2.7.3, Summary of Clinical Efficacy – CABP, Table 6.2.3.2-1.

13.10. Line listing for the subjects experiencing serious adverse events during the Group 1 studies

Table 57 Serious Adverse Event Listing - Group 1 Studies.

Unique Subject Identifier	Age (y)	Sex	Race	Country	Actual Treatment	Study Day of Start of AE	Body System or Organ Class	Dictionary Derived Term	Reported Term	Causality By Investigator
Study P903-23										
P903-23.001523001	1.2	F	WHITE	USA	Ceftaroline	19	Infections and infestations	Pneumonia viral	Viral pneumonia	N
P903-23.006323001	15	F	WHITE	USA	Ceftaroline	44	Infections and infestations	Clostridium difficile colitis	Clostridium difficile enterocolitis	Y
P903-23.021923002	12	F	WHITE	POL	Ceftaroline	9	Immune system disorders	Hypersensitivity	Allergic reaction	Y
P903-23.170123003	11	M	WHITE	LVA	Ceftaroline	5	Infections and infestations	Osteomyelitis	Osteomyelitis	N
P903-23.180223007	3	F	WHITE	LTU	Comparator	30	Blood and lymphatic system disorders	Lymphadenitis	Acute inflammation of mesenteric lympnodes	N
P903-23.180223007	3	F	WHITE	LTU	Comparator	21	Infections and infestations	Tonsillitis	Purulent 149 onsillitis, hospital treatment	N
Study P903-31										
P903-31.002331001	2	M	WHITE	USA	Ceftaroline	12	Infections and infestations	Pneumonia respiratory syncytial viral	RSV Pneumonia	N
P903-31.021931013	3	F	WHITE	POL	Ceftaroline	16	Infections and infestations	Infectious pleural effusion	Phyothorax	N
P903-31.140931001	5	M	WHITE	HUN	Ceftaroline	8	Metabolism and nutrition disorders	Dehydration	dehydration	N
P903-31.140931001	5	M	WHITE	HUN	Ceftaroline	8	Infections and infestations	Gastroenteritis	gastroenteritis	N
P903-31.141331004	4	F	WHITE	HUN	Ceftaroline	12	Infections and infestations	Gastroenteritis	gastroenteritis	N

P903-31.141731006	1.2	M	WHITE	HUN	Ceftaroline	29	Infections and infestations	Bronchitis	Obstructive bronchitis.	N
P903-31.141731008	6	F	WHITE	HUN	Ceftaroline	21	Infections and infestations	Pneumonia	Long lasting left side peumonia.	N
P903-31.202931001	4	M	WHITE	USA	Comparator	29	Respiratory, thoracic and mediastinal disorders	Pulmonary thrombosis	Left Lower Lobe (lung) Thrombus	N
Study P903-24										
P903-24.120924001	5	F	WHITE	GEO	Comparator	42	Infections and infestations	Viral upper respiratory tract infection	Independent Viral Infection, Upper Respiratory Tract	N
P903-24.120924001	5	F	WHITE	GEO	Comparator	42	Infections and infestations	Lower respiratory tract infection viral	Independent Viral Infection, Lower Respiratory Tract	N

13.11. Line listing for the subjects experiencing serious adverse events during the Group 2 studies

Table 58 Serious Adverse Event Listing – Group 2 Studies.

Unique Subject Identifier	Age	Sex	Race	Actual Treatment	End Date Time of Treatment	Start Date Time of Adverse Event	Body System or Organ Class	Dictionary Derived Term	Reported Term for the Adverse Event	Causality By Investigator
P903-21.01021004	9 DAYS	F	WHITE	Ceftaroline	2012-11-08 T19:41	2012-11-09 T07:17	Blood and lymphatic system disorders	Anaemia neonatal	ANEMIA OF PREMATURITY	N
P903-21.01121005	8 YEARS	M	WHITE	Ceftaroline	2011-05-02 T20:25	2011-05-05 T20:15	Skin and subcutaneous tissue disorders	Rash	RASH (WORSENING OF SKIN RASH)	N
P903-21.02021003	611 DAYS	M	WHITE	Ceftaroline	2012-03-06 T10:03	2012-03-08 T13:21	Nervous system disorders	Tremor	TREMORS	N
P903_15-0003-15001	13 YEARS	M	White	Ceftaroline	2008-08-22 T15:02	2008-09-03 T14:00	Musculoskeletal and connective tissue disorders	Pathological fracture	PATHOLOGIC RT HUMERUS FRACTURE	Unrelated

*All study subjects enrolled in USA.

13.12. Reasons for study and study drug discontinuation in the Group 1 studies

Table 59 Reasons for Discontinuation From Study Drug and Study.

	Study P903-23		Study P903-31 and P903-24		Study P903-23, P903-31 and P903-24 Pooled	
Reason for Discontinuation from Study Drug	**Ceftaroline fosamil (n=106)**	**Comparator (n=53)**	**Ceftaroline fosamil (n=151)**	**Comparator (n=49)**	**Ceftaroline fosamil (n=257)**	**Comparator (n=102)**
Total	*7 (6.6%)*	*5 (9.4%)*	*13 (8.6%)*	*4 (8.2%)*	*20 (7.8%)*	*9 (8.8%)*
Adverse Event	2 (1.9%)	2 (3.8%)	4 (2.6%)	0 (0%)	6 (2.3%)	2 (2.0%)
Insufficient therapeutic effect	0 (0%)	0 (0%)	6 (4.0%)	3 (6.1%)	6 (2.3%)	3 (2.9%)
Lost to Follow-up	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)
Other Reasons	0 (0%)	2 (3.8%)	2 (1.3%)	1 (2.0%)	2 (0.8%)	3 (2.9%)
Request of sponsor or investigator	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)
Withdrawal of Consent	3 (2.8%)	0 (0%)	1 (0.7%)	0 (0%)	4 (1.6%)	0 (0%)
Reason for Discontinuation from Study	**Ceftaroline fosamil (n=106)**	**Comparator (n=53)**	**Ceftaroline fosamil (n=151)**	**Comparator (n=49)**	**Ceftaroline fosamil (n=257)**	**Comparator (n=102)**
Total	*4 (3.8%)*	*4 (7.5%)*	*5 (3.3%)*	*1 (2.0%)*	*9 (3.5%)*	*5 (4.9%)*
Did not Meet Inc/Exc Criteria	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)
Lost to Follow-up	0 (0%)	2 (3.8%)	1 (0.7%)	1 (2.0%)	1 (0.4%)	3 (2.9%)
Other Reasons	1 (0.9%)	0 (0%)	3 (2.0%)	0 (0%)	4 (1.6%)	0 (0%)
Withdrawal of Consent	3 (2.8%)	1 (1.9%)	1 (0.7%)	0 (0%)	4 (1.6%)	1 (1.0%)

13.13. TEAEs leading to study drug discontinuation in the Group 1 studies

Table 60 Treatment Emergent Adverse Events Leading to Study Drug Discontinuation – Group 1 Studies.

	Study P903-23		Study P903-31 and P903-24		Study P903-23, P903-31 and P903-24 Pooled	
Body System or Organ Class/ Dictionary Derived Term	**Ceftaroline fosamil (n=106)**	**Comparator (n=53)**	**Ceftaroline fosamil (n=151)**	**Comparator (n=49)**	**Ceftaroline fosamil (n=257)**	**Comparator (n=102)**
Total	*4 (3.8%)*	*2 (3.8%)*	*6 (4.0%)*	*0 (0%)*	*10 (3.9%)*	*2 (2%)*
Gastrointestinal disorders	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Vomiting	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Immune system disorders	1 (0.9%)	1 (1.9%)	0 (0%)	0 (0%)	1 (0.4%)	1 (1%)
Drug hypersensitivity	0 (0%)	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Hypersensitivity	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Infections and infestations	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)
Osteomyelitis	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Gastrointestinal viral infection	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Investigations	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Aspartate aminotransferase increased	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Alanine aminotransferase increased	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Nervous system disorders	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Headache	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Skin and subcutaneous tissue disorders	1 (0.9%)	0 (0%)	3 (2.0%)	0 (0%)	4 (1.6%)	0 (0%)
Rash	1 (0.9%)	0 (0%)	1 (0.7%)	0 (0%)	2 (0.8%)	0 (0%)
Rash macular	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Urticaria	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Vascular disorders	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Kawasaki's disease	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)

13.14. Line listing for the subjects discontinuing study drug due to a TEAE in the Group 1 studies

Table 61 Discontinuation of Study Drug Due to Adverse Event Listing – Group 1 Studies.

Unique Subject Identifier	Country	Sex	Age (y)	Race	Treatment	Adverse Event Start/ End Day	Body System or Organ Class	Dictionary Derived Term	Reported Term for the Adverse Event	Serious Event	Causality by Investigator
Study P903-23											
P903-23.001123002	USA	F	14	WHITE	Ceftaroline	8/12	Skin and subcutaneous tissue disorders	Rash	rash	N	Y
P903-23.002323001	USA	M	2	WHITE	Comparator	4/5	Gastrointestinal disorders	Vomiting	vomiting	N	Y
P903-23.021923002	POL	F	12	WHITE	Ceftaroline	9/12	Immune system disorders	Hypersensitivity	Allergic reaction	Y	Y
P903-23.070723004	ARG	M	11	WHITE	Comparator	1/1	Immune system disorders	Drug hypersensitivity	Allergic reaction associated with the passage of study medication.	N	Y
P903-23.130523006	ESP	F	2	WHITE	Ceftaroline	7/8	Infections and infestations	Gastrointestinal viral infection	gastrointestinal virus that causes vomiting and fever	N	N
P903-23.170123003	LVA	M	11	WHITE	Ceftaroline	5/?	Infections and infestations	Osteomyelitis	Osteomyelitis	Y	N
Study P903-31											
P903-31.021931015	POL	M	8	WHITE	Ceftaroline	3/19	Vascular disorders	Kawasaki's disease	Kawasaki disease	N	N
P903-31.061231002	BGR	F	7	WHITE	Ceftaroline	1/1	Nervous system disorders	Headache	headache,	N	Y

						1/1	Nervous system disorders	Headache	headache	N	Y
P903-31.141731014	HUN	M	1.8	WHITE	Ceftaroline	7/8	Skin and subcu-taneous tissue disorders	Urticaria	Urticaria	N	Y
Study P903-24											
P903-24.001124001	USA	M	4	WHITE	Ceftaroline	8/20	Inves-tigations	Alanine amino-transferase increased	elevated ALT	N	Y
						8/15	Inves-tigations	Aspartate amino-transferase increased	elevated AST	N	Y
P903-24.001124002	USA	M	17	WHITE	Ceftaroline	8/10	Skin and subcu-taneous tissue disorders	Rash macular	erythemat ous macular rash on face, trunk and extremitie s	N	Y
P903-24.002324001	USA	M	5	WHITE	Ceftaroline	8/14	Skin and subcu-taneous tissue disorders	Pruritus	Itching	N	Y
						8/14	Skin and subcu-taneous tissue disorders	Rash	rash	N	Y

13.15. Analysis for Significant Adverse Events

Table 62 Incidence of Treatment-emergent Adverse Events of Hypersensitivity/Anaphylaxis by System Organ Class and Preferred Term Across the Completed Active-controlled Studies—Safety Population.

System Organ Class *Preferred Term*	*ABSSSI* *Study P903-23*		*CABP* *Studies P903-24 and P903-31*		*Pooled Studies* *P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106) n (%)	*Comparators (N = 53) n (%)*	*Ceftaroline (N = 151) n (%)*	*Comparators (N = 49) n (%)*	*Ceftaroline (N = 257) n (%)*	*Comparators (N = 102) n (%)*
Subjects with at least 1 TEAE of hypersensitivity/anaphylaxis	*15 (14.2)*	*6 (11.3)*	*13 (8.6)*	*6 (12.2)*	*28 (10.9)*	*12 (11.8)*
Immune system disorders						
Hypersensitivity	1 (0.9)	0	0	0	1 (0.4)	0
Drug hypersensitivity	0	1 (0.9)	0	0	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders						
Bronchospasm	0	0	1 (0.7)	0	1 (0.4)	0
Skin and subcutaneous tissue disorders						
Rash	8 (7.5)	2 (3.8)	5 (3.3)	0	13 (5.1)	2 (2.0)
Rash macular	1 (0.9)	0	2 (1.3)	0	3 (1.2)	0
Urticaria	0	0	3 (2.0)	1 (2.0)	3 (1.2)	1 (1.0)
Dermatitis allergic	2 (1.9)	1 (1.9)	0	0	2 (0.8)	1 (1.0)
Dermatitis contact	0	1 (1.9)	2 (1.3)	0	2 (0.8)	1 (1.0)
Rash maculo-papular	1 (0.9)	0	1 (0.7)	0	2 (0.8)	0
Eczema	1 (0.9)	0	0	1 (2.0)	1 (0.4)	1 (1.0)
Urticaria papular	1 (0.9)	0	0	0	1 (0.4)	0
Dermatitis	0	0	0	1 (2.0)	0	1 (1.0)
Dermatitis atopic	0	0	0	1 (2.0)	0	1 (1.0)
Rash erythematous	0	0	0	1 (2.0)	0	1 (1.0)
Red man syndrome	0	1 (0.9)	0	1 (2.0)	0	2 (2.0)

Percentages are calculated as 100 × (n/N).
Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; N = number of subjects in the Safety Population; n = number of subjects within a specific category; TEAE = treatment-emergent adverse event.
Source: Appendix Table 3.6.1.2.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety, Table 5.1.6.2.1-1.

Table 63 Incidence of Treatment Emergent Adverse Events from Broad SMQ* Search Pseudomembranous Colitis in Group 1 Studies – Safety Population.

	Study P903-23		Study P903-31 and P903-24		Study P903-23, P903-31 and P903-24 Pooled	
Dictionary Derived Term	**Ceftaroline (n=106)**	**Comparator (n=53)**	**Ceftaroline (n=151)**	**Comparator (n=49)**	**Ceftaroline (n=257)**	**Comparator (n=102)**
Total	*9 (8.5%)*	*9 (17.0%)*	*12 (8.0%)*	*3 (6.1%)*	*21 (8.2%)*	*12 (11.8%)*
Clostridium difficile colitis	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Clostridium difficile infection	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Diarrhoea	9 (8.5%)	9 (17.0%)	12 (8.0%)	2 (4.1%)	21 (8.2%)	11 (10.8%)
Diarrhoea haemorrhagic	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)
Enteritis	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)	0 (0%)	1 (1.0%)

**MedDRA version 17.0 used.*

Table 64 Incidence of Treatment Emergent Adverse Events from Broad SMQ* Search Eosinophilic Pneumonia in Group 1 Studies – Safety Population.

	Study P903-23		Study P903-31 and P903-24		Study P903-23, P903-31 and P903-24 Pooled	
Dictionary Derived Term	**Ceftaroline (n=106)**	**Comparator (n=53)**	**Ceftaroline (n=151)**	**Comparator (n=49)**	**Ceftaroline (n=257)**	**Comparator (n=102)**
Total	*7 (6.6%)*	*1 (1.9%)*	*7 (4.6%)*	*1 (2.0%)*	*14 (5.5%)*	*2 (2.0%)*
Asthma	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Bronchial hyperreactivity			1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Bronchospasm	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Eosinophil count increased	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)
Eosinophilia	5 (4.7%)	1 (1.9%)	1 (0.7%)	0 (0%)	6 (2.3%)	1 (1.0%)
Hypoxia	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)	0 (0%)	1 (1.0%)
Pneumonia	1 (0.9%)	0 (0%)	1 (0.7%)	0 (0%)	2 (0.8%)	0 (0%)
Wheezing	1 (0.9%)	0 (0%)	1 (0.7%)	0 (0%)	2 (0.8%)	0 (0%)

**MedDRA version 17.0 used.*

Table 65 Incidence of Treatment-emergent Adverse Events of Drug Induced Liver Injury by System Organ Class and Preferred Term Across the Completed Active-controlled Studies—Safety Population.

System Organ Class / *Preferred Term*	*ABSSSI Study P903-23*		*CABP Studies P903-24 and P903-31*		*Pooled Studies P903-23, P903-24, and P903-31*	
	Ceftaroline (N = 106) n (%)	*Comparators (N = 53) n (%)*	*Ceftaroline (N = 151) n (%)*	*Comparators (N = 49) n (%)*	*Ceftaroline (N = 257) n (%)*	*Comparators (N = 102) n (%)*
Subjects with at least 1 TEAE of potential drug induced liver injury	**1 (0.9)**	**1 (1.9)**	**7 (4.6)**	**3 (6.1)**	**8 (3.1)**	**4 (3.9)**
Hepatobiliary disorders						
Hypertransaminasaemia	0	0	1 (0.7)	0	1 (0.4)	0
Investigations						
Aspartate aminotransferase increased	1 (0.9)	0	4 (2.6)	1 (2.0)	5 (1.9)	1 (1.0)
Alanine aminotransferase increased	1 (0.9)	1 (1.9)	3 (2.0)	2 (4.1)	4 (1.6)	3 (2.9)
Transaminases increased	0	0	2 (1.3)	1 (2.0)	2 (0.8)	1 (1.0)

Percentages are calculated as 100 × (n/N).

Abbreviations: ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; N = number of subjects in the Safety Population; n = number of subjects within a specific category; TEAE = treatment-emergent adverse event.

Source: Appendix Table 3.6.1.5.

Source: NDA 200327 Module 2.7.4 Summary of Clinical Safety, Table 5.1.6.5.1-1.

13.16. Selected Treatment Emergent Adverse Events by System Organ Class for Pooled Group 1 Pediatric Studies and Pooled Adult Phase 3 Studies Occurring at ≥ 2%

Table 66 Selected Treatment Emergent Adverse Events by System Organ Class for Pooled Group 1 Pediatric Studies and Pooled Adult Phase 3 Studies Occurring at ≥ 2%.

	Pooled Phase 3 Pediatric Clinical Trials (Group 1 Studies)[1]		Pooled Phase 3 Adult Clinical Trials (two in ABSSSI and two in CABP)[2]	
System Organ Class/ Treatment Emergent Adverse Events	**Ceftaroline (N=257) n (%)**	**Comparators (N=102) n (%)**	**Ceftaroline (N=1305)[3] n (%)**	**Pooled comparators (N=1301)[3] n (%)**
Blood and lymphatic system disorders	**16 (6.2%)**	**8 (7.8%)**	**25 (1.9%)**	**24 (1.8%)**
Esoinophilia	6 (2.3%)	1 (1.0%)	1 (0.1%)	0
Anemia	6 (2.3%)	1 (1.0%)	12 (0.9%)	15 (1.2%)
Thrombocytosis	3 (1.2%)	4 (3.9%)	1 (0.1%)	1 (0.1%)
Gastrointestinal Disorders	**43 (16.7%)**	**23 (22.5%)**	**173 (13.3%)**	**145 (11.1%)**
Diarrhea*	20 (7.8%)	10 (9.8%)	60 (4.6%)	42 (3.2%)
Vomiting*	13 (5.1%)	12 (11.8%)	27 (2.1%)	20 (1.5%)
Nausea*	8 (3.1%)	1 (1.0%)	55 (4.2%)	49 (3.8%)
Constipation*	3 (1.2%)	2 (2.0%)	27 (2.1%)	24 (1.8%)
General disorders and administration site conditions	**18 (7.0%)**	**9 (8.8%)**	**91 (7.0%)**	**93 (7.1%)**
Pyrexia	8 (3.1%)	2 (2.0%)	13 (1.0%)	21 (1.6%)
Infections and infestations	**40 (15.6%)**	**18 (17.6%)**	**116 (8.9%)**	**131 (10.1%)**
Gastroenteritis	4 (1.6%)	1 (1.0%)	2 (0.2%)	4 (0.3%)
Laboratory Investigations	**11 (4.3%)**	**7 (6.9%)**	**96 (7.4%)**	**95 (7.3%)**
Aspartate aminotransferase increased	5 (1.9%)	1 (1.0%)	11 (0.8%)	9 (0.7%)
Alanine aminotransferase increased	4 (1.6%)	3 (2.9%)	13 (1.0%)	18 (1.4%)

	Pooled Phase 3 Pediatric Clinical Trials (Group 1 Studies)[1]		Pooled Phase 3 Adult Clinical Trials (two in ABSSSI and two in CABP)[2]	
System Organ Class/ Treatment Emergent Adverse Events	**Ceftaroline (N=257) n (%)**	**Comparators (N=102) n (%)**	**Ceftaroline (N=1305)[3] n (%)**	**Pooled comparators (N=1301)[3] n (%)**
Metabolism and Nutrition Disorders	**8 (3.1%)**	**6 (5.9%)**	**73 (5.6%)**	**82 (6.3%)**
Hypocalcemia	1 (0.4%)	2 (2.0%)	0	0
Hypokalemia*	0	1 (1.0%)	24 (1.8%)	30 (2.3%)
Hyperphosphatemia	0	2 (2.0%)	0	0
Nervous System Disorders	**9 (3.5%)**	**2 (2.0%)**	**95 (7.3%)**	**80 (6.1%)**
Headache	6 (2.3%)	1 (1.0%)	57 (4.4%)	40 (3.1%)
Psychiatric disorders	**3 (1.2%)**	**1 (1.0%)**	**58 (4.4%)**	**57 (4.4%)**
Insomnia	1 (0.4%)	0	36 (2.8%)	31 (2.4%)
Anxiety	1 (0.4%)	0	6 (0.5%)	9 (0.7%)
Respiratory, thoracic and mediastinal disorders	**18 (7.0%)**	**8 (7.8%)**	**63 (4.8%)**	**91 (7.0%)**
Cough	4 (1.6%)	3 (2.9%)	5 (0.4%)	6 (0.5%)
Skin and Subcutaneous Tissue Disorders	**38 (14.8%)**	**15 (14.7%)**	**88 (6.7%)**	**123 (9.5%)**
Rash*	13 (5.1%)	2 (2.0%)	24 (1.8%)	19 (1.5%)
Pruritus	4 (1.6%)	3 (2.9%)	25 (1.9%)	59 (4.5%)
Pruritus generalized	0	0	15 (1.1%)	18 (1.5%)
Vascular Disorders	**4 (1.6%)**	**1 (1.0%)**	**71 (5.4%)**	**67 (5.1%)**
Phlebitis*	0	0	20 (1.5%)	18 (1.4%)

[1]For a full listing of all TEAEs reported in the pediatric Group 1 studies, please refer to the Summary of Clinical Safety, Appendix Table 3.1.1.1.
[2]For a full listing of all TEAEs reported in the pooled Phase 3 adult trials, please refer to the Integrated Summary of Safety Appendix Table 4.1.2.3.1.
[3]Note that denominators used for pooled adult studies are slightly different on the current label than shown in this table, where the safety population is used.
**Preferred Term listed in current label, Table 4: Adverse Reactions Occurring in ≥ 2% of Patients Receiving Teflaro in the Pooled Phase 3 Clinical Trials.[1]*

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/s/

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