Cross-Discipline Team Leader Review

Date	May 25, 2016
From	Hala Shamsuddin MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	200327/S16 and S17
Applicant	Cerexa Inc. (Subsidiary of Forest Laboratories LLC.)
Date of Submission	December 7, 2015
PDUFA Goal Date	June 7, 2016
Proprietary Name / Established (USAN) names	Teflaro®/ceftaroline fosamil
Dosage forms / Strength	Powder for Intravenous Injection/400 and 600 mg vials
Approved Indication(s)	1. Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) 2. Treatment of Community-Acquired Bacterial Pneumonia (CABP)
Proposed Actions	Expanding both approved indications in adults to the pediatric population 2 months to less than 18 years of age
Recommended:	Approval

1. Introduction

Ceftaroline fosamil (Teflaro®) is the prodrug of ceftaroline, a cephalosporin antibacterial drug. Teflaro was approved on October 29, 2010 in adults 18 years of age or older for the treatment the following:

- Acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca.*
- 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 initially approved dose in adults was 600 mg administered intravenously (IV) over 60 minutes every 12 hours. The duration of administration was changed from 60 minutes to a range of 5 to 60 minutes based on the results of a pharmacokinetic (PK) study in adults (NDA 200237/ S-14, approved August 31, 2015). Dosing adjustment is recommended in adult patients with moderate-severe renal impairment.

In this supplemental NDA (sNDA) , the Applicant proposes to expand the two approved indications to include the pediatric population 2 months to <18 years of age. In support of this

proposal, the Applicant submitted data from a population PK modeling update and target attainment simulation for ceftaroline for children birth to less than 18 years of age (CPT-MS-08), a single dose PK study in pediatric subjects 12 to 17 years of age (Study P903-15), a single dose PK study in pediatric patients birth to less than 12 years of age (Study P903-21), and three randomized, active-controlled clinical trials in children 2 months to less than 18 years, one study in ABSSSI (Study P903-23) and two in hospitalized children with CABP (Study P903-31) and complicated CABP (Study P903-24). The clinical trials were not powered for statistical inferential testing, but were mainly designed to assess safety, as efficacy of ceftaroline will be extrapolated from adults since disease pathogenesis, clinical features and causative bacterial organisms are similar in adults and children.

In the pediatric clinical studies, ceftaroline fosamil dosing regimen was as described in Table 1 and infused over 60 minutes (Studies P903-23 and P903-31) or over 120 minutes (Study P903-24). In this submission, the Applicant proposes ceftaroline dosing regimen as described in Table 1 and the duration of infusion in children to mirror that in adults, i.e. 5 to 60 minutes, however, there were no clinical studies to assess the PK, tolerability or safety of a 5 minute infusion in pediatric patients. Additionally, because of insufficient PK data, dosing adjustment in pediatric patients with moderate-severe renal impairment was not proposed.

2. Background

Regulatory Background

At the time of approval of Teflaro in October 2010, five post-marketing requirements (PMRs) were requested pursuant to the Pediatric Research Equity Act (PREA):

- **PMR 1692-001**: Single dose pharmacokinetic trial evaluating safety of Teflaro in pediatric patients in five age cohorts – (6 years to less than 12 years, 24 months to less than 6 years, 28 days to less than 24 months, term neonates less than 28 days and pre-term neonates less than 28 days.
- **PMR 1692-002**: Comparative trial of Teflaro in pediatric patients less than 17 years of age with CABP enriching for patients with MRSA. A minimum of 150 patients receiving Teflaro should be enrolled.
- **PMR 1692-003**: Comparative trial of Teflaro in pediatric patients less than 17 years of age with ABSSSI including patients with suspected or documented MRSA. A minimum of 150 patients receiving Teflaro should be enrolled.
- **PMR 1692-004**: Evaluate cerebrospinal fluid concentrations in infants less than 2 months of age. A minimum of 12 patients should be enrolled
- **PMR 1692-005**: Comparative trial of Teflaro in pediatric patients less than 2 months of age with ABSSSI or CABP including suspected or documented MRSA.

In April 2011, the FDA agreed to enrolling 120 ceftaroline recipients in the CABP study and 180 ceftaroline recipients in the ABSSSI study in April 2011.

In the current submission, Study P903-21 addresses PMR 1692-001, Studies P903-31 and P903-24 address PMR 1692-002, and Study P903-23 addresses PMR 1692-003.

(b) (4)

Acute Bacterial Skin and Skin Structure Infections
ABSSSI include cellulitis/erysipelas, wound infection, major cutaneous abscess and burn infections. *Staphylococcus aureus* (SA) is the most common cause of ABSSSI encountered in the outpatient or inpatient setting. Other causes of ABSSSI include *Streptococcus pyogenes, S. agalactiae*, other streptococcal species, and gram-negative rods.

Clinical course, disease pathogenesis, bacterial etiologies and susceptibility profiles of the bacterial agents of ABSSSI are similar in adults and children, allowing extrapolation of efficacy from adults if the dosing regimen results in similar exposures.

Community Acquired Bacterial Pneumonia
CABP is an acute bacterial infection of the pulmonary parenchyma that may manifest 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. "Typical" causes for CABP include *S. pneumoniae, Hemophilus influenzae, Klebsiella* species and *S. aureus*. Pulmonary complications of CABP include pleural effusion, empyema, pneumothorax, lung abscess, bronchopleural fistula, necrotizing pneumonia and respiratory failure.

Clinical course, disease pathogenesis, bacterial etiologies and susceptibility profiles of the bacterial agents of CABP are similar in adults and children, allowing extrapolation of efficacy from adults if the dosing regimen results in similar exposures.

3. CMC/Device

No new CMC information was submitted in this supplement.

4. Nonclinical Pharmacology/Toxicology

Dr. Amy Ellis, PhD performed the pharmacology/toxicology review.
Reproductive and developmental toxicity studies and genotoxicity studies were submitted and reviewed at the time of the initial NDA approval.

In this supplement, the Applicant submits 14 day pharmacology/toxicology studies in neonatal and juvenile rats. Doses of ceftaroline fosamil up to 270 mg/kg (the highest dose tested) given to neonatal rats intravenously from postnatal day 7 to day 21 were not associated with clinical signs of toxicity. Renal cysts were noted in the kidneys of both control and ceftaroline exposed rats, more so in males. These cysts were not considered an adverse finding as they were present in a relatively small portion of animals and were not associated with reduced renal function.

Of note, the 270 mg/kg dose resulted in Cmax and AUC0-t that were 28-fold higher and 2-3 fold higher than the predicted Cmax and median steady state AUC respectively for the proposed clinical dosing regimen.

Dr. Ellis recommended approval of this sNDA for ceftaroline use in patients 2 months to less than 18 years of age with ABSSSI or CABP.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Kunyi Wu, PharmD performed the clinical pharmacology review. Her findings are summarized.

The Applicant conducted two single dose PK studies in pediatric patients: Study P903-15 in children 12 to 17 years of age and Study P903-21 from birth to less than 12 years of age. PK data from these two studies and from the clinical studies P903-23, P903-31 and P903-24 that were conducted in pediatric patients 2 months to less than 18 years of age with ABSSSI or CABP were used to update the population PK model that was developed using the data from adults. The updated population PK model was used to conduct simulations to predict ceftaroline exposures and PK/PD target attainment in pediatric patients by age and renal function. Because PK data were available for only one pediatric patient with CrCL <50mL/min/1.73m^2, the Applicant was unable to propose dosing adjustment for pediatric patients with moderate-severe renal impairment. The dosing regimen used in the clinical studies and the Applicant's proposed dosing regimen are shown in Table 1.

Table 1: Ceftaroline Fosamil Dosing Regimen Used in Pediatric Clinical Studies and Proposed Dosing Regimen for Labeling

Study	Dosing Regimen Used in Clinical Studies	Proposed Regimen for Labeling
P903-23	IV over 60 minutes every 8 hrs 2- <6 months: 8 mg/kg ≥6 months weighing ≤33 kg: 12 mg/kg ≥6 months weighing >33 kg: 400 mg	IV over 5 to 60 minutes every 8 hrs 2 - <24 months: 8 mg/kg 24 mo -<18 yrs weighing ≤33kg: 12 mg/kg 24 mo -<18 yrs weighing >33kg: 400 mg
P903-24	IV over 120 minutes every 8 hrs 2- <6 months: 10 mg/kg ≥6 months weighing ≤40 kg: 15 mg/kg ≥6 months weighing >40 kg: 600 mg	
P903-31	IV over 60 minutes every 8 hrs 2- <6 months: 8 mg/kg ≥6 months weighing ≤33 kg: 12 mg/kg ≥6 months weighing >33 kg: 400 mg	

The PK/PD target parameter that is associated with efficacy for cephalosporins is the percentage of the duration of unbound drug concentration above MIC in each dosing interval (%fT > MIC). Target attainment simulation indicated that the dose regimens proposed by the Applicant following 5 or 60 minute infusion were predicted to result in %fT > MIC values similar to or greater than for adult subjects dosed with the currently approved dose of 600 mg every 12h following 5 or 60 minute infusion for MIC values up to (b) (4) and 0.5 mg/L for *S pneumoniae*.

In all three age cohorts, based on simulation results, the 5 minute infusion in pediatric patients would result in approximately 50% higher Cmax compared to the 60 minute infusion within the same age group (Table 2). However, the 5 minute and 60 minute infusions resulted in similar steady state AUC (AUC24,ss) (Table 3). Compared to adults receiving the same infusion duration, the proposed doses for pediatric patients were simulated to result in 10-80% higher AUC24,ss, and either similar to up to 45% higher Cmax,ss (Table 3). In 12 to <18 years of age receiving the proposed dosing regimen over 5 minutes or 60 minutes, PK parameters were overall similar to the PK in adults.

Table 2: Comparison of Similated Median Cmax,ss between the Infusion Time of 5 Minutes and 1 Hour with the Applicant's Proposed Doses

12 mg/kg q8h (2-<18 years) and > 33 kg: 400 mg q8h			
Age group	Cmax,ss 1hr infusion (mg/L)	Cmax,ss 5 min infusion (mg/L)	Ratio (5min/1hr)
12-17 yrs	19.7	25.7	1.3
6-12yrs	27.6	37.4	1.4
2-6 yrs	27.1	38.4	1.4
8 mg/kg q8h (2months -< 2 years)			
Age group	Cmax,ss 1hr infusion (mg/L)	Cmax,ss 5 min infusion (mg/L)	Ratio (5min/1hr)
18-24 m	18.8	26.3	1.4
12-18 m	19.1	26.4	1.4
6-12 m	19.6	26.6	1.4
2-6 m	19.2	25.1	1.3

Source: Clinical Pharmacology Review, Table 3

Table 3: Simulated Median (90% PI) Ceftaroline AUC24,ss and Cmax,ss by Age following the Applicant's Proposed Doses and Infusion Time

		AUC24,ss (mg*hr/L) (90% PI)		Cmax,ss (mg/L) (90% PI)	
renal function	Age	Duration of Infusion		Duration of Infusion	
		5 min	1 hr	5 min	1 hr
normal (>80 mL/min/1.73m2)	12-<18 years	122 (73.8, 203)	122 (72.7, 201)	25.7 (13.1, 50.7)	19.7 (11.0, 34.2)
	6-<12 years	157 (99.7, 247)	157 (99.7, 245)	37.4 (20.0, 69.2)	27.6 (16.4, 43.3)
	2-<6 years	144 (92.2, 222)	144 (92.6, 225)	38.4 (21.2, 68.7)	27.1 (16.8, 41.8)
	18-<24 months	107 (69.2, 166)	107 (69.0, 165)	26.3 (14.7, 46.8)	18.8 (11.8, 29.1)
	12-<18 months	112 (71.9, 174)	113 (71.8, 174)	26.4 (14.9, 47.5)	19.1 (11.9, 29.4)
	6-<12 months	121 (78.1, 188)	120 (78.3, 188)	26.6 (14.9, 46.9)	19.6 (12.2, 30.0)
	2-<6 months	134 (86.5, 209)	134 (86.6, 208)	25.1 (14.4, 44.0)	19.2 (12.1, 29.7)
mild (>50, ≤80 mL/min/1.73m2)	12-<18 years	136 (81.6, 226)	136 (80.9, 227)	26.5 (13.7, 51.2)	20.7 (11.5, 35.6)
	6-<12 years	175 (109, 276)	175 (110, 276)	38.2 (20.5, 69.8)	28.8 (17.0, 45.4)
	2-<6 years	160 (101, 249)	160 (102, 252)	39.3 (22.0, 69.6)	28.3 (17.5, 44.0)
	18-<24 months	133 (82.6, 218)	133 (82.8, 219)	27.6 (15.5, 49.6)	20.6 (12.8, 32.3)
	12-<18 months	140 (85.9, 228)	140 (86.0, 227)	27.7 (15.6, 49.1)	20.9 (13.0, 32.6)
	6-<12 months	152 (92.6, 247)	152 (92.6, 247)	27.9 (16.0, 49.7)	21.4 (13.3, 33.3)
	2-<6 months	168 (104, 275)	168 (103, 275)	26.6 (15.3, 46.5)	21.2 (13.2, 33.3)
adults 600 mg q12h, normal renal function	adults	97.5 (59.2, 164)	97.1 (58.8, 164)	26.5 (13.6, 52.0)	20.9 (11.7, 36.6)

Source: Clinical Pharmacology Review, Table 1

Dr. Wu noted that safety of the 5 minute infusion is supported in the 6 months to less than 2 years age group. In this age group, the Cmax,ss of the proposed dosing regimen of 8 mg/kg every 8 hours administered over 5 minutes is similar to or lower than the Cmax,ss of the dose regimen administered in the pediatric clinical studies of 12 mg/kg given over 60 minutes every 8 hours.

Dr. Wu concluded that the proposed doses for patients 2 months to less than 18 years of age with ABSSSI or CABP and normal renal function or mild renal impairment are acceptable. The one hour infusion duration was acceptable for all ages. From a clinical pharmacology perspective, the five minute duration was acceptable for children 6 months of age or older. Dr. Wu stated that there were no data to support the PK, tolerability or safety of the 5 min infusion in children 2 months to less than 6 months of age and recommended additional data in this population.

I concur with Dr. Wu regarding the acceptability of the proposed doses for patients 2 months to less than 18 years of age for ABSSSI or CABP. Regarding the duration of infusion, Cmax after the 5 minute infusion was, as expected, higher than Cmax after the 60 minute infusion in children of all age groups. The ratio of such increase was the same in all age groups (Tables 2 and 3). The Cmax in pediatric patients 2 months to less than 6 months of age after the 5 minute infusion was in the same range as that in adults, adolescents and pediatric patients 6 months to 2 years of age [median approximately 26 mg/L (range approximately 15, 51)], in whom safety is supported by the clinical studies. Additionally, the Cmax in pediatric patients 2 months to less than 6 months of age is lower than the Cmax in pediatric patients 2 years to less than 12 years of age [median approximately 38 mg/L (range approximately 21, 68)] (Table 3). The exposure resulting from this dose is lower than the mean Cmax observed in single dose PK studies in adults of 81.4, 80.7 and 105.6 mg/L after doses of 1500, 1500 and 2000 mg, respectively (n=69). Given the half-life of ceftaroline, the duration of Cmax exposure is relatively short (less than one hour), and there is extensive prior experience with the cephalosporin drug class in children. The preclinical studies did not indicate specific safety concerns at exposures that were approximately 28-fold higher than the anticipated human exposure. It should also be noted that administration over 5 minutes is a worst case scenario and that 5 minute to 60 minute infusion duration would allow for greater flexibility in a healthcare setting.

For all the above reasons, I conclude that another PK/safety study in children 2 months to less than 6 months of age is unlikely to provide additional safety/dosing information, and that continued postmarketing pharmacovigilance would suffice.

As PK simulations indicate that pediatric patients weighing more than 33 kg and whose dose is capped at 400 mg every 8 hours may receive the adult dose of 600 mg every 12 hours, labeling will include this alternative dosing regimen.

6. Clinical Microbiology

Dr. Avery Goodwin performed the clinical microbiology review.

The Applicant submitted ceftaroline susceptibility data for the relevant pathogens of ABSSSI and CABP obtained from clinical specimens in 70 medical centers across the United States. MIC_{50} and MIC_{90} of these isolates were similar to isolates collected from adult patients.

In the ABSSSI study (Study P903-23), the highest ceftaroline MIC against *S. aureus* was 1 mcg/ml (range 0.06-1 mcg/ml) and the highest MIC against *S. pyogenes* was 0.015 mcg/ml (range 0.008 - 0.015 mcg/ml). A favorable microbiological outcome at TOC was reported as 94.2% for ceftaroline vs 81.8% for the comparator in the microbiologic modified intent-to-treat (mMITT) population.

Limited susceptibility data were obtained from the CABP study as only 7% had a typical respiratory pathogen isolated. However, favorable microbiologic outcome was achieved in 79.2% of ceftaroline- treated patients and 77.8% of comparator-treated patients.

Dr. Goodwin concluded that MIC_{90} values for ceftaroline against the indicated pathogens do not appear to have significantly changed since the approval of ceftaroline in 2010 and remain at or below the susceptible breakpoints in the package insert. He recommended approval of this sNDA.

7. Clinical/Statistical- Efficacy

Drs. Dan Rubin Ph.D. and Sheral Patel MD conducted the efficacy evaluation. Their findings are summarized.

ABSSSI

Study P903-23 was a multicenter, randomized, observer-blinded, active controlled descriptive study that evaluated the safety and tolerability of ceftaroline fosamil in children 2 months to <18 years of age with ABSSSI as defined in the 2013 FDA Guidance for Industry with the 75 cm^2 lesion area required for adults adjusted for body surface area in children. Patients were randomized to receive ceftaroline fosamil `or active comparator (vancomycin or cefazolin, depending on the prevalence of MRSA at the study site) in 2:1 ratio. Randomization was stratified by age cohort (cohort 1: 12 yrs to <18 yrs, cohort 2: 6 yrs to <12 yrs, cohort 3: 24 months to < 6 yrs, and cohort 4: 2 months to <24 months) and region. Patients with CrCL<50mL/min/1.73 m^2 and patients who received more than 24 hours of prior effective antibacterial therapy were excluded.

Ceftaroline fosamil dosing is as in Table 1. A switch to oral cephalexin, clindamycin or linezolid was allowed on or after Day 4 if pre-defined criteria for clinical response were met. The total duration of therapy was 5-14 days.

There was no specified primary endpoint and no formal inferential statistical hypothesis testing as efficacy will be extrapolated from adults. Three definitions were used for clinical response at Study Day 3: at least 20% reduction in total infection area from baseline, cessation of spread in the total infection area relative to baseline, or cessation of spread as measured by length and width and resolution of fever. Clinical cure (defined as resolution of all signs and

symptoms of ABSSSI or improvement to such an extent that further antibacterial therapy was not required) at end of IV therapy, end of overall therapy and at test-of-cure visit, clinical and microbiologic outcomes by organism and clinical relapse at late follow up visit were also evaluated. The primary analysis population was the modified intent-to-treat (MITT) population (randomized and received at least one dose of study drug).

One hundred and sixty three (163) patients were enrolled, 110 to receive ceftaroline and 53 to receive active comparator. The MITT population included 107 in the ceftaroline arm and 52 in the active comparator arm.

In the MITT population, in the ceftaroline arm, 23 patients were included in age cohort 1, 36 in age cohort 2, 23 in age cohort 3 and 25 in age cohort 4. Approximately 85% were white, and 23% Hispanic. Fifty-seven (53.3%) were male. Approximately two-thirds had cellulitis. Approximately 30% had a drainage or debridement procedure. Approximately 50% had no organism identified, and 40% were due to *S. aureus* (approximately 17% MRSA and 23% MSSA), with *S. pyogenes* accounting for approximately 12% and GNR for 2.8%. Overall, patient baseline characteristics were balanced in the two treatment arms.

Clinical outcomes and comparison with adult trials are described in Table 4.

Table 4: Clinical Responses/Clinical Outcome in Pediatric and Adult Patients with ABSSSI

	Pediatric (Study P903-23)			Adult (Studies P903-06 &P903-07)	
	Ceftaroline	**Comparator**	**Difference (95% CI)**	**Ceftaroline**	**Comparator**
Day 3: ≥20% reduction from baseline infection area					
Responder	91/107 (85%)	44/52 (85%)	0% (11%,14%)	Not analyzed	
Day 3: Cessation of spread by total infection area					
Responder	98/107 (92%)	47/52 (91%)	1% (-8%,13%)	369/400 (92.3%)	358/397 (90.2%)
Day 3: Cessation of spread by infection length and width and temperature <37.6°C					
Responder	86/107 (81%)	39/52 (75%)	5% (-8%,20%)	296/400 (74.0%)	263/397 (66.2%)
Clinical Outcome					
Clinical Cure at TOC	101/107 (94%)	45/52 (87%)	8% (-1%,20%)	595/693 (85.9%)	586/685 (85.5%)

Source: Adapted from Table 6, Statistical Review and Table 10 MO review

Approximately 5-8% of patients evaluated on Day 3 had incomplete data/indeterminate responses. Only one patient in the comparator arm was classified as clinical failure; the other patients not classified as clinical cure were lost to follow up or had other extenuating circumstances precluding classification. The clinical responses on Day 3 and clinical cure at TOC visit seemed similar to those noted in the adult studies.

The point estimates for clinical response/cure were similar across all age cohorts; however, sample sizes in each age cohort were small resulting in wide confidence intervals.

Dr. Rubin noted that efficacy evaluation is limited due to the lack of pre-specified primary analysis. Additionally, the degree of possible measurement error for skin lesions in pediatrics and the meaningfulness of cessation of lesion spread or 20% reduction in area are unknown. However, efficacy data did not raise any specific concerns.

CABP

The Applicant conducted two studies: P903-31 and P903-24.

Study P903-31 was multicenter, randomized, observer-blinded and active-controlled with the primary objective of evaluating safety and tolerability in children 2 months to less than 18 years of age with CABP as defined by the 2014 FDA Guidance to Industry and requiring hospitalization. Patients with CrCL < 50 mL/min/1.73 m^2 or who had received >24 hours of prior effective antibacterial therapy were excluded. Patients were randomized 3:1 to receive ceftaroline fosamil (dosed similar to ABSSSI study, Table 1) or ceftriaxone. Randomization was stratified by age cohort similar to the ABSSSI study. A switch to oral therapy with amoxicillin/clavulanate on or after Day 4 was allowed if pre-defined criteria for improvement were met. Total duration of therapy was 5-14 days.

Study P903-24 was similar to Study P903-31 but enriched for patients with complicated CABP or at high risk for infection with MRSA. Patients with *P. aeruginosa* infection were excluded. Additionally, ceftaroline was dosed differently (Table 1) based on PK/PD modeling for *S. aureus* infection, vancomycin was added to ceftriaxone in the comparator arm, oral switch was allowed to amoxicillin/clavulanate, clindamycin or linezolid, and total duration of therapy was 5 to 21 days.

Neither study was powered for efficacy/comparative inferential statistical testing. Dr. Rubin pooled the two studies to increase sample size because both studies were descriptive, Study P903-24 had only 9 patients in the comparator arm, the study design, randomization ratio, procedures and endpoint definition were similar and there was no obvious heterogeneity in results. Additionally, although Study P903-24 enriched for MRSA, no patient with MRSA was enrolled in either trial. Dr. Patel reviewed each study separately but included the pooled results in her review. This summary will focus on the pooled results for the reasons provided by Dr. Rubin.

The MITT (randomized and received at least one dose and had confirmed CABP caused by a typical pathogen) population was the primary efficacy analysis population. Efficacy outcome measures included clinical response on Day 4, clinical outcome at end of IV therapy, end of overall therapy, and at test of cure and late follow up visits, and clinical and microbiologic outcomes by pathogen. Clinical response on Day 4 was defined as improvement in at least 2 symptoms and worsening of none of the following symptoms compared to baseline: cough, dyspnea, sputum production, chest pain, chills or rigors, feeling of warmth/feverishness, and exercise tolerance or lethargy. Clinical cure was defined as resolution of all signs and

symptoms of CABP or improvement to such an extent that further antimicrobial therapy is not required.

The MITT population included 107 and 29 subjects in the ceftaroline arms and 36 and 9 in the comparator arms in Study P903-31 and P903-24 respectively. In the ceftaroline arm, 11 were in age cohort 1, 26 in age cohort 2, 70 in age cohort 3 and 29 in age cohort 4. Approximately 57% were male, and 97% were white. Patient demographics and disease characteristics were similar in the two arms. Approximately 79% had CrCL $\geq$ 80 mL/min/1.73m^2 and the rest had CrCL between 50 and 80 mL/min/1.73m^2. Approximately 36% had multi-lobar involvement. Only 7% had a typical respiratory pathogen isolated from respiratory culture. *S. pneumoniae* urinary antigen was positive in 20%.

Clinical response on Day 4 is shown in Table 5. No patient had a relapse at the late follow up visit in either study. Although numbers were small, clinical responses on Day 4 and clinical cure at TOC visit seemed similar between the age cohorts. The number of baseline pathogens isolated was too small to allow any meaningful conclusions regarding response by pathogen.

Table 5: Clinical Responses/Outcome in Pediatric and Adult Patients with CABP

	Pediatric Studies P903-31 & P903-24			Adult Studies P903-08 & P903-09	
	Ceftaroline	**Comparator**	**Difference (95% CI)**	**Ceftaroline**	**Comparator**
Day 4 Clinical Response					
Responder[a]	89/136 (65%)	30/45 (67%)	-1% (-16% to 15%)	106/151 (70.2%)	90/153 (58.8%)
Day 4 Clinical Stability					
Stability	43/136 (31%)	15/45 (33%)	-2% (-18% to 13%)		
Clinical Outcome					
Clinical Cure at TOC[b]	120/136 (88%)	41/45 (91%)	-3% (-12% to 10%)	479/580 (82.6%)	439/573 (76.6%)

Source: Adapted from Table 8 Statistics Review and Table 11 MO Review

a. MITT analysis population for pediatric studies, FDA-defined microbiologic modified intent-to-treat mMITT for adult studies

b. MITT (modified intent to treat) population used for pediatric studies, MITTE (modified intent to treat efficacy) population used for adult studies.

Dr. Rubin noted that the limitations of the above results include lack or pre-specified primary analysis, and confidence intervals that did not guarantee ceftaroline tightly preserved the efficacy of the control regimen. However, the efficacy results did not raise specific concerns.

Dr. Patel reached the same conclusions for both indications.

Dr. Rubin and Dr. Patel recommended approval of this sNDA to expand the approved indications to include children 2 months to less than 18 years of age. They recommended describing the pediatric study results the Clinical Studies section of labeling for Study P903-23 under the ABSSSI indication and agreed with the Applicant to only include Study P903-31 for

the CABP indication since Study P903-24 enriched for MRSA infection, and ceftaroline is not approved for the treatment of CABP due to MRSA in adults.

I concur with their findings and recommendations.

8. Safety

Dr. Sheral Patel MD performed the safety review for the ABSSSI (ceftaroline n = 106) and the pooled CABP studies (ceftaroline n = 151) and pooled (total 257), and for the single dose PK studies. Her findings are summarized.

The safety database consisted of 257 children who received multiple ceftaroline fosamil doses in Studies P903-23, P903-31 and P903-24, and 62 children who received a single dose in the PK studies. One hundred and two patients received a comparator. The mean and median duration of ceftaroline exposure in the pooled comparative clinical studies were 6.4 and 6.0 days respectively. Although not shown in Table 6, the duration of exposure and the proportion of patients in each age cohort who switched to oral therapy were similar in the ceftaroline and comparator arms.

Table 6: Ceftaroline Multiple Dose Exposure in Pediatric Clinical Studies P903-23, P903-31 and P903-24

	ABSSSI Study P903-23 N = 106	CABP Studies P903-31 and P903-24 N = 151	Study P903-23 P903-31 and P903-24 N = 257
Ceftaroline Exposure (days)			
Mean ceftaroline days	5.8 (2.5)	6.7 (3.0)	6.4 (2.9)
Median ceftaroline days	5.0 (2-14)	6.0 (1-19)	6.0 (1-19)
Ceftaroline Doses			
Median	12.0 (3-41)	15.0 (2-54)	15.0 (2-54)
Switched to oral drug	65 (61.3%)	101 (66.9%)	166 (64.6%)
Age			
12 yrs to < 18 yrs	23 (21.7%)	13 (8.6%)	36 (14.0%)
6 yrs to <12 yrs	36 (34.0%)	33 (21.9%)	69 (26.8%)
24 mo to <6 yrs	23 (21.7%)	76 (50.3%)	99 (38.5%)
2 mo to <24 mo	24 (22.6%)	29 (19.2%)	53 (20.6%)
Sex			
Males	56 (52.8%)	85 (56.3%)	141 (54.9%)

Source: Modified from Applicant submission, Summary of Clinical Safety, Tables 4.2.1-1 and 4.3.1-1 and MO review Tables 13 and 14

There were no meaningful differences in IV drug exposure or total drug (IV plus oral switch) between ceftaroline and comparators, and no meaningful differences in proportions of patients in the various age cohorts or by sex and race.

Table 7: Summary of Adverse Events noted in Pediatric Clinical Studies P903-23, P903-31 and P903-24

	ABSSSI P903-23 N = 106	CABP P903-31 and P903-24 N = 151	Study P903-23 P903-31 and P903-24 N = 257	Comparator N = 102
Deaths	0	0	0	0
Serious Adverse Event	4 (3.8%)	6 (4.0%)	10 (3.9%)	3 (2.9%)
Adverse Event Leading to Discontinuation	4 (3.8%)	6 (4.0%)	10 (3.9%)	2 (2.0%)
Any Treatment Emergent Adverse Event	51 (48.1%)	67 (44.4%)	118 (45.9%)	49 (48.0%)

Source: Applicant Submission, Clinical Overview, Table 5.3-1

There were no deaths in any of the pediatric studies. SAEs occurred in 10/257 (3.9%) in pooled ceftaroline recipients and 3/102 in comparators (2.9%). SAEs in ceftaroline recipients were mainly in MedDRA Infections and Infestations System Organ Class (SOC) but included two that were judged to be drug-related (hypersensitivity reaction described as angioedema and generalized maculopapular rash and *C. difficile* infection). Four patients in the PK studies experienced SAE, none probably related to study drug.

Ten patients (3.9%) in the pooled studies discontinued ceftaroline because of an adverse event (4 ABSSSI and 6 CABP), compared to 2 (2.0%) in the comparator arm. Of these 10 patients, four were due to skin reactions (3 rash, one urticaria) and one due to elevated transaminases.

Standard MedDRA Queries (SMQ) were conducted for specific AEs included in the Warnings and Precautions section of Teflaro® labeling, including hypersensitivity reactions, *C. difficile* infection and positive direct Coombs' test. SMQs were also conducted for AEs noted in the postmarketing section (bone marrow suppression, eosinophilic pneumonia) and for AEs that occur with the cephalosporin class (seizures, renal impairment and drug-induced liver injury). Overall, the frequency of hypersensitivity reactions and *C. difficile* infection were similar in the ceftaroline and comparator arms, but the incidence of Coomb's positive test was higher in ceftaroline recipients than in the comparator (17.2% vs. 2.7%) and also higher compared to adults (17.2% vs. 10.7%). Less than 3% of patients had elevated transaminases and no case satisfied Hy's law. Leukopenia was reported in one patient. There were no cases of eosinophilic pneumonia, hemolytic anemia, convulsions, or renal impairment.

Treatment emergent adverse events (TEAE) occurring in ≥ 3% of ceftaroline recipients included diarrhea (7.8%), vomiting (5.1%), rash (5.1%), nausea (3.1%) and pyrexia (3.1%). Additional AEs that occurred in ≥2% of ceftaroline recipients included abdominal pain,

increased ALT and pruritus. Overall, the pattern and frequency of TEAEs were similar to the comparators.

The number of patients in each age cohort was too small to allow conclusions regarding age-specific AEs. There were no apparent differences in safety findings between males or females. The majority of patients were white; no conclusions could be reached regarding any ethnicity or race specific AEs.

Dr. Patel concluded that no new safety signals were identified in the pediatric population that were not already included in Teflaro labeling. She recommended updating the Warnings and Precautions section with the frequency of occurrence of Coombs' positive test, similar to the information for adults. Additionally, she recommended updating the Adverse Reactions section with a table of AEs noted in ≥3% of pediatric patients enrolled in the pooled ABSSSI and CABP studies, and adding leukopenia to the post-marketing section due to reports received for this adverse reaction.

I concur with Dr. Patel's recommendations.

Dr. Patel noted that ceftaroline was infused in the clinical studies over 60 minutes or 120 minutes. However, the Applicant proposes duration of 5 to 60 minutes in labeling. She stated that this proposal is acceptable and does not raise specific safety concerns due to lack of safety concerns in adults (where the 5 min infusion results in higher Cmax compared to the 60 min infusion) and to the fact that no adverse events were noted in animal studies at 20-28 fold higher exposure and the extensive clinical experience with beta-lactams.

Dr. Patel recommended approval of this sNDA to expand the approved indications to pediatric patients 2 months to 18 years of age. I concur with her recommendation.

9. Advisory Committee Meeting

This sNDA was not discussed at an advisory committee meeting.

10. Pediatrics

This submission was discussed with the Pediatric Review Committee (PeRC) on April 27, 2016. The committee discussed the issue of the higher Cmax achieved for infusion duration of 5 minutes since the pediatric studies were conducted with infusion duration of 60 or 120 minutes. The committee felt that knowledge of the safety profile of the cephalosporin class and postmarketing data in adults subsequent to the labeling change regarding shortening the infusion duration can be leveraged, and deferred to the Division regarding the need for further safety assessments.

(b) (4) Studies P903-31 and P903-24 fulfills PMR 1692-002, and Study P903-23 fulfills PMR 1692-003.

Studies in neonates up to 2 months of age (PMRs 1692-004 and 1692-005) remain pending.

11. Other Relevant Regulatory Issues

The Applicant submitted the required financial disclosures except for principal investigators for the ABSSSI study at sites 702 and 804. These sites enrolled a total of seven patients (6.5% of the MITT population). Conclusions regarding efficacy or safety analyses were not affected by including or excluding these seven patients.

The Office of Study Integrity and Surveillance (OSIS) inspected the analytic sites for the PK Studies P903-15 and P903-21. These studies were conducted at Forest Research Institute, Inc., in Farmingdale, New York. Since Forest Research Institute was acquired by Actavis, the audit was conducted with the archived records at the Actavis facility in Elizabeth, New York. No objectionable issues were identified and FDA From 483 was not issued. The inspector, Dr. Sripal Mada, Ph.D., concluded that the analytical portions of the audited studies are reliable and recommended accepting the data for further Agency review.

OSIS also inspected the analytic sites for the bioanalytical portions of Studies P903-23, P903-24 and P903-31. These were conducted at (b) (4) . An initial 3-item Form 483 was issued, to which the site responded with additional data. The final classification for the inspection was Voluntary Action Indicated (VAI). The inspector, Dr. Gopa Biswas, Ph.D., recommended that the data from the bioanalytical portion of these studies be accepted for further Agency review.

12. Labeling

The following sections in Teflaro® labeling will be updated:

Indications and Usage: to expand the patient population to include pediatric patients 2 months to less than 18 years of age for both approved indications.

Dosage and Administration: to include the Applicant's proposed dosage recommendations for pediatric patients with normal renal function, and include 600 mg every 12 hours as an alternative dose to 400 mg every 8 hours for those weighing more than 33 kg. There are no data to include recommendations for pediatric patients with moderate-severe renal impairment (CrCL<50 mL/min/1.73m^2).

Warnings and Precautions: update the warning regarding positive Coombs' test to include the frequency of occurrence in the pediatric population.

Adverse Reactions: Add table of adverse events noted in ≥3% of children enrolled in the pediatric trials P903-23, P903-24 and P903-31, the AEs noted in less than 2% that were not included in the adult AE list (increased ALT, pruritus), and the term leukopenia to the post-marketing section.

Use in Specific Populations: the Pregnancy and Lactation sections were updated in compliance with PLLR, and the Pediatric Use section was updated to include description of the pediatric efficacy and safety data for both indications.

Clinical Studies: updated with description of the pediatric studies, clinical response rate on Day 3 for ABSSSI (defined as resolution of fever and cessation of lesion spread), clinical response rate on Day 4 for CABP, and clinical cure rates for both indications.

13. Recommendations/Risk Benefit Assessment

The recommendation is to approve this sNDA 200327/S 16 and 17 to expand the approved indications of Teflaro® (ceftaroline fosamil) for the treatment of ABSSSI and CABP to include pediatric patients 2 months to less than 18 years of age.

Efficacy in pediatrics is being extrapolated from adults based on the similarity of disease pathophysiology, causative bacterial pathogens and susceptibility pattern of the implicated pathogens. While the clinical studies were descriptive, clinical response rates for ceftaroline fosamil in the treatment of ABSSSI and CABP in the conducted randomized, active-control pediatric trials seemed similar to those observed in adults across all age cohorts.

In the pediatric clinical studies, ceftaroline fosamil was administered over 60 or 120 minutes. The Applicant proposed the duration of administration to be 5 to 60 minutes, similar to the duration of infusion recommended for adults. The proposed pediatric dosing regimens given over 5 or 60 minute were predicted to result in %fT > MIC values for the target organisms that were similar to or greater than for adults dosed with the currently approved dose of 600 mg every12 hours following 5 or 60 minute infusion. Administration over 5 minutes in pediatric patients was simulated to result in approximately 50% higher Cmax compared to the 60 minute infusion in all age cohorts, and in similar or up to 45% higher Cmax compared to 5 minute infusion in adults. After 5 minute infusion, the median Cmax in children 2 mo to <6 mo age was similar to that in adults, children 6 mo to < 2 years of age and 12 to 18 years of age, and lower than the median Cmax in children 2 years to 12 years of age. The safety profile noted in pediatric patients was similar to the safety profile noted in adults and similar to the safety profile noted for cephalosporins. No new safety signals emerged that warranted additions to the Warnings and Precautions section.

Overall, the risk/benefit of ceftaroline in the treatment of both labeled indications is as favorable in children as it is in adults. A Risk Evaluation and Mitigation Strategy is not required, as all the safety signals are labeled and no new signals emerged.

This sNDA fulfills PMR 1692-002 and PMR 1692-003.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HALA H SHAMSUDDIN
05/26/2016

SUMATHI NAMBIAR
05/26/2016
I agree with Dr. Shamsuddin's conclusions and recommendations.