NDA Multidisciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	200327
Priority or Standard	Standard
Submit Date(s)	November 13, 2018
Received Date(s)	November 13, 2018
PDUFA Goal Date	September 13, 2019
Division/Office	Division of Anti-Infective Products Office of Antimicrobial Products
Review Completion Date	September 4, 2019
Established/Proper Name	Ceftaroline fosamil
Trade Name	Teflaro
Pharmacologic Class	Cephalosporin class of beta-lactams
Code name	PPI-0903 (also known as TAK-599)
Applicant	Allergan Sales, LLC
Dosage form	Injection
Applicant proposed Dosing Regimen	6 mg/kg every 8 hours as a (b) (4)-minute infusion in patients <2 months of age (b) (4)
Applicant Proposed Indication(s)/Population(s)	No new proposed indication. Updated labeling in Section 8.4 for patients less than 2 months of age.
Regulatory Action	Approval
Indication(s)/Population(s) (if applicable)	Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in pediatric patients 0* to less than 2 months old (*Gestational age 34 weeks and older and postnatal age 12 days and older)
Dosing Regimen	6 mg/kg every 8 hours by IV infusion administered over 30 to 60 min

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Glossary

ABSSSI	Acute Bacterial Skin and Skin Structure Infections
AE	adverse event
CABP	community-acquired bacterial pneumonia
CNS	central nervous system
CRP	C-reactive protein
CSF	cerebrospinal fluid
DAIP	Division of Anti-Infective Products
DSUR	Development Safety Update Report
EOT	End-of-Therapy
FDA	Food and Drug Administration
GA	gestational age
HCT	hematocrit
IND	investigational new drug
IV	intravenous
ITT	intent-to-treat
LLOQ	lower limit of quantification
LOS	late-onset sepsis
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
Micro-ITT	microbiological ITT
mITT	modified ITT
NDA	new drug application
OCP	Office of Clinical Pharmacology
OSI	Office of Scientific Investigation
PADER	Periodic Adverse Drug Experience Report
PD	pharmacodynamics
PeRC	Pediatric Research Committee
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
sNDA	supplemental new drug application
TEAE	treatment-emergent adverse event
TOC	Test-of-Cure

1 Executive Summary

1.1. Product Introduction

Ceftaroline fosamil (Teflaro) is a sterile, semisynthetic, prodrug of ceftaroline, a cephalosporin antibacterial drug with activity against gram-positive and gram-negative bacteria.

Ceftaroline fosamil is currently approved for the treatment of adult and pediatric patients 2 months of age and older for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).

This supplemental new drug application (sNDA) was submitted to fulfill PREA PMR 1692-005 to: "Perform a randomized comparison of ceftaroline and comparator in infants <2 months of age with ABSSSI and CABP including patients with infections suspected or demonstrated to be caused by MRSA." The data to support fulfillment of this postmarketing requirement (PMR) are from Study P903-26, "Open-label, Multicenter Study to Evaluate the Safety, Tolerability, PK, and Efficacy of Ceftaroline in Neonates and Young Infants with Late-Onset Sepsis."

***M.O. Comment**: On 1/23/18, the Division informed the Applicant that Study P903-26 combined with population pharmacokinetics/pharmacodynamics (PK/PD) modeling and simulation data could potentially support dosing recommendations in infants <2 months of age for the treatment of ABSSSI. Due to differences in the etiology and pathophysiology of CABP in pediatric patients <2 months of age, efficacy findings from adult and pediatric patients ≥2 months of age cannot be extrapolated to infants <2 months of age.*

1.2. Conclusions on the Substantial Evidence of Effectiveness

The safety and effectiveness of Teflaro in infants <2 months of age were evaluated in a single study that enrolled 11 pediatric patients with a gestational age of ≥34 weeks and a postnatal age of 12 days to less than 2 months of age with known or suspected infections. The majority of patients (8 of 11) received 6 mg/kg Teflaro every 8 hours as an intravenous (IV) infusion over 60 minutes. A finding of efficacy for this pediatric population is based on extrapolation from adult and older pediatric (≥2 months of age) patients and pharmacokinetic model-based analyses demonstrating similar ceftaroline exposure in adults and the proposed pediatric population down to 34 weeks gestational age and 12 days postnatal age, using a dose of 6 mg/kg as a 30- to 60-minute infusion every 8 hours. Safety findings in these 11 pediatric patients were limited, but similar to those observed in adult and pediatric patients 2 months of age and older.

1.3. Patient Experience Data

Patient experience data were not submitted as part of this application.

2 Therapeutic Context

2.1. Analysis of Condition

2.1.1. Acute Bacterial Skin and Skin Structure Infections

In the first few weeks of life, 40% to 50% of neonates are colonized by *S. aureus* and nasal carriage may be an important risk factor for *S. aureus* infections.[1,2] Hospitalized neonates, especially preterm and low birthweight infants are at higher risk of development of staphylococcal infections likely due to an immature immune system, invasive procedures, and long hospital stays.[3] One study of nosocomial infections (NIs) among neonates in high-risk nurseries in 99 U.S. hospitals reported that 6-10% (varying by birthweight category) of the NIs were skin and soft tissue infections with 31% of these due to *S. aureus*.[4] Authors have reported on recent outbreaks of skin and soft tissue infections caused by *S. aureus* in neonates.[5,6]

2.2. Analysis of Current Treatment Options

2.2.1. ABSSSI

The following antibacterial drugs are indicated for the treatment of skin and skin structure infections (SSSI) or complicated skin and skin structure infections (cSSSI) down to birth, or do not have a lower age limit for the indication.

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[1] Peacock SJ, Justice A, Griffiths D, de Silva GD, Kantzanou MN, Crook D, et al. Determinants of acquisition and carriage of Staphylococcus aureus in infancy. J Clin Microbiol. 2003;41:5718–25.
[2] Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005;5:751–62.
[3] Healy CM, Palazzi DL, Edwards MS, Campbell JR, Baker CJ. Features of invasive staphylococcal disease in neonates. Pediatrics. 2004;114:953–61.
[4] Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infections Surveillance System. Pediatrics. 1996;98:357–61.
[5] Pimentel de Araujo F, et al. An outbreak of skin infections in neonates due to a Staphylococcus aureus strain producing the exfoliative toxin A. Infection. 2018 Feb;46(1):49-54.
[6] Sanchini A, et al. Outbreak of skin and soft tissue infections in a hospital newborn nursery in Italy due to community-acquired methicillin resistant Staphylococcus aureus USA300 clone. J Hosp Infect. 2013;83:36–40.

Table 1. Summary of Approved Antibacterial Drugs for Treatment of ABSSSI or Related Indications in Neonates

Product(s) Name	Relevant Indication	Dosing/ Administration	Important Safety and Tolerability Issues
Amoxicillin	SSSI	Oral	Hypersensitivity reactions
Amoxicillin and clavulanate potassium	SSSI	Oral	Hypersensitivity reactions, hepatotoxicity
Ceftazidime	SSSI	IV	Hypersensitivity reactions, seizures
Cefotaxime	SSSI	IV	Hypersensitivity reactions
Clindamycin	SSSI	Oral and IV	*Clostridium difficile*-associated diarrhea, warning statement that the drug does not adequately diffuse into the CSF and should not be used in the treatment of meningitis
Gentamicin	Skin and soft tissue infections	IV	Nephrotoxicity, neurotoxicity (ototoxicity, neuromuscular blockage, respiratory paralysis)
Amikacin	Skin and soft tissue infections	IV	Nephrotoxicity, neurotoxicity (ototoxicity, neuromuscular blockage, respiratory paralysis)
Tobramycin	Skin, bone, and skin-structrue infections	IV	Nephrotoxicity, neurotoxicity (ototoxicity, neuromuscular blockage, respiratory paralysis)
Vancomycin	SSSI	IV	Infusion reactions, nephrotoxicity
Linezolid	cSSSI	Oral and IV	Myelosuppression, peripheral and optic neuropathy, serotonin syndrome

SSSI = skin and skin structure infections; cSSSI = complicated skin and skin structure infections

Other antibacterial drugs approved for gram-postive infections prior to the distinction of indications specific for skin and skin structure infections include oxacillin, dicloxacillin, and nafcillin.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ceftaroline (ceftaroline fosamil, Teflaro) was approved on 29 October 2010 (NDA 200327) for treatment of ABSSSI and CABP in adults. On 27 May 2016, a supplemental NDA was approved to include the use of ceftaroline in pediatric patients 2 months to less than 18 years of age for ABSSSI and CABP.

3.2. Summary of Presubmission/Submission Regulatory Activity

At the time of initial NDA approval, the Applicant was assigned the following Pediatric Research Equity Act (PREA) Postmarketing Requirements (PMR): 1692-004 and 1692-005.

PMR 1692-004: Perform a trial assessing the cerebrospinal fluid (CSF) concentration profile of ceftaroline 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.

Final protocol submission: May 2014
Trial completion date: September 2016
Final report submission: March 2017

PMR 1692-005: Perform a randomized comparison of ceftaroline and comparator in infants <2 months of age with ABSSSI and CABP including patients with infections suspected or demonstrated to be caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Final protocol submission: May 2014
Trial completion date: September 2016
Final report submission: March 2017

For both PMR 1692-004 and PMR 1692-005, a deferral extension request was submitted to FDA on 06 September 2016 citing slow study enrollment and recruitment challenges. The Agency granted a due date extension for the trial completion date and final submission date on 25 January 2017. The original trial completion and final submission dates of September 2016 and March 2017 were extended to December 2017 and December 2018, respectively.

On 03 November 2017, the Applicant submitted a Type B Written Responses Only meeting request due to continued challenges in enrollment and recruitment. The Applicant proposed to close Study P903-26 by 31 December 2017 based on the neonatal data generated up to that date. The Applicant also requested an agreement to submit an sNDA consisting of the clinical study report for Study P903-26 with data collected up until 31 December 2017 and population PK/PD modeling and simulation data to fulfill PMR 1692-004 and 1692-005.

A meeting with the Pediatric Research Committee (PeRC) was held on 17 January 2018. The PeRC agreed with the Division to release PMR1692-004 because the study was not feasible. In addition, the PeRC recommended no deferral extension for PMR1692-005 and Applicant submission of data collected to date for review.

On 23 January 2018, the Division issued a letter to the Applicant communicating the release of PREA PMR 1692-004 and advising the Applicant to submit an sNDA with Study P903-26 and population PK/PD modeling report for PREA PMR 1692-005 to potentially support dosing recommendations and labeling for infants <2 months of age for treatment of ABSSSI.

Based on Division feedback, the Applicant completed Study P903-26 on 30 December 2017.

3.3. Office of Scientific Investigations

No clinical study site inspection was conducted.

The analytical site that processed the PK samples was recently inspected by the Office of Study Integrity and Surveillance in association with other NDAs. The investigator found that the data from the audited studies were reliable, and the final inspection classification was No Action Indicated.

3.4. Product Quality

There were no updates to Drug Substance/Drug Product in support of this application. Therefore, there is no Module 3 of this supplement.

3.5. Clinical Microbiology

There were no updates to clinical microbiology in support of this application.

4 Nonclinical Pharmacology/Toxicology

A 14-day intravenous toxicity study with ceftaroline was conducted in neonatal rats. Up to 270 mg/kg/day was administered intravenously from postnatal day 7 to 21. Half of the animals were sacrificed the day after dosing was completed and the other half was sacrificed following a 4-week recovery period. This study was reviewed under NDA 200327 SUPPL-016. It is adequate to support the current application as well.

No clinical signs of toxicity were observed and hematology and clinical chemistry did not show drug-related differences compared to controls. A functional observational battery conducted on PND 28 did not reveal neurobehavioral differences between the groups that were related to ceftaroline. Renal cysts, located primarily in the cortex, were observed at higher than expected incidences in both control and ceftaroline-treated rats. In males, the incidence of the finding was higher in the 90 and 270 mg/kg dose groups compared to controls, but the incidence of cysts in kidneys from ceftaroline-treated females did not clearly differ from controls when the data from both the PND 22 (end of dosing) and PND 50 (recovery) sacrifices were considered. The sponsor did not consider the cysts to be an adverse finding because they were present only in a small portion of the kidney and did not appear to compromise renal function based on results of clinical chemistry testing. The etiology of renal cysts is not well understood. There may be a genetic predisposition to the formation of these cysts. In this study, it is possible that they were related to infusion since they observed at higher than expected incidences in control animals as well as those that received ceftaroline fosamil.

5 Clinical Pharmacology

5.1. Executive Summary

The Applicant's initial proposed dose for this age group was 6 mg/kg every 8 hours by intravenous (IV) infusion administered over (b) (4) min. From a clinical pharmacology perspective, the pharmacokinetics information in this sNDA is acceptable to support the approval of ceftaroline for patients from 0 to <2 months of age with ABSSSI. (b) (4) Therefore, the Applicant revised the infusion time to 30 to 60 minutes in these patients. From a Clinical Pharmacology perspective, the proposed range of 30 to 60 minutes for the infusion time is acceptable.

The recommended doses in labeling for different age groups are listed below.

- Adult patients >18 years of age: 600 mg every 12 hours by IV infusion administered over 5 to 60 min
- Pediatric patients from 2 years to <18 years of age weighing ≤33 kg: 12 mg/kg every 8 hours by IV infusion administered over 5 to 60 min. Pediatric patients from 2 years to <18 years of age weighing >33 kg: 400 mg every 8 hours or 600 mg every 12 hours by IV infusion administered over 5 to 60 min
- Pediatric patients from 2 months to <2 years of age: 8 mg/kg every 8 hours by IV infusion administered over 5 to 60 min

Two clinical studies (Table 2) were conducted in pediatric patients age from birth to two months who received ceftaroline fosamil and sparse PK samples were collected in these patients.

Table 2. Clinical Studies in Pediatric Patients Age From Birth to 2 Months who Received Ceftaroline Fosamil

Study Number	Study Title	Postnatal Age Range
P903-21	Pharmacokinetics of a Single Dose of Ceftaroline fosamil in Children Ages Birth to Younger than 12 Years With Suspected or Confirmed Infection	Birth to <12 years
P903-26 (C2661002)	Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline in Neonates and Young Infants with Late-Onset Sepsis (LOS)	Birth to <2 months (i.e., postnatal age 12 days to 53 days)

*By the Clinical Pharmacology reviewer

The clinical pharmacology information provided by the Applicant in support of this application is found to be acceptable and supports the approval of sNDA 200327.

5.2. Summary of Clinical Pharmacology Assessment

5.2.1. Study P903-26

Study P903-26 was an open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline in neonates and young infants with late-onset sepsis (LOS). The study is described in detail in Section 6.1 Table of Clinical Studies and Section 7.1 Review of Relevant Studies.

The primary objectives were to evaluate the pharmacokinetic (PK) profile and efficacy of ceftaroline in neonates and young infants aged 7 to <60 days with LOS.

Methodology

The study consisted of three age cohorts 1, 2, and 3 where four, five, and two patients were enrolled, respectively:

- Cohort 1: Young infants aged >28 days to <60 days (N=4)
- Cohort 2: Term neonates aged 7 to ≤28 days (N=5)
- Cohort 3: Preterm neonates aged 7 to ≤28 days (N=2)

Ceftaroline fosamil was initially given at a dose of 4 mg/kg IV over 60 (±10) minutes q8h (±1 hour); however, in the second protocol amendment, the dose of ceftaroline fosamil was increased to 6 mg/kg. Three subjects received 4 mg/kg IV q8h and provided PK samples (one subject in each cohort) prior to protocol amendment 2. The total duration of ceftaroline treatment was 48 hours (minimum) to 14 days (maximum). Hospitalization was required during IV study treatment.

Two PK blood samples (approximately 0.3 to 0.6 mL per draw) were obtained at steady state from the patients at any time between the end of the fourth infusion of ceftaroline fosamil and before the end of treatment (EOT) or Study Day 14 (whichever was earlier). Patients were randomly assigned (1:1) at the time of enrollment to one of the PK sample collection schedules:

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

PK analysis was conducted in the PK analysis set. Ceftaroline plasma concentration data, along with other information including demographic data, were combined with appropriate data from other clinical studies and analyzed using a population PK approach and reported separately.

Bioanalytical Validation and Assay

The following section details the bioanalytical method validation for the analysis of ceftaroline, ceftaroline fosamil, and ceftaroline open ring metabolite in human plasma by HPLC with MS/MS detection based on the final validation report submitted on 21 December 2018.

Table 3. Summary of Analytical Methods for Quantification of Ceftaroline, Ceftaroline fosamil, and Ceftaroline Open Ring Metabolite (ORM) in Human Plasma*

Information Requested	Data
Analyte	Ceftaroline, ceftaroline fosamil, ceftaroline open ring metabolite (ORM)
Internal standard (IS)	D3-ceftaroline, d3-ceftaroline fosamil, d3-ceftaroline ORM
Method description	Protein precipitation / LC-MS/MS
Limit of quantitation	Ceftaroline: 0.0500 to 50.0 µg/mL Ceftaroline fosamil and ceftaroline ORM: 0.0500 to 10.0 µg/mL
Standard curve concentrations (units/mL)	Ceftaroline: 0.05, 0.10, 1.00, 2.00, 4.00, 8.00, 20.00, 42.00, 50.00 µg/mL Ceftaroline fosamil: 0.05, 0.10, 0.20, 0.40, 0.80, 1.60, 4.00, 8.40, 10.0 µg/mL Ceftaroline ORM: 0.05, 0.10, 0.20, 0.40, 0.80, 1.60, 4.00, 8.40, 10.0 µg/mL
QC concentrations (units/mL)	Ceftaroline: 0.0500 µg/mL, 0.150 µg/mL, 2.40 µg/mL, 40.0 µg/mL, 60.0 µg/mL Ceftaroline fosamil and Ceftaroline ORM: 0.0500 µg/mL, 0.150 µg/mL, 1.20 µg/mL, 8.00 µg/mL, 20.0 µg/mL
Bench-top stability (hrs)	2 hours on wet ice
Processed stability (hrs)	Ceftaroline and Ceftaroline fosamil: 109 hours at 2 to 8°C Ceftaroline ORM: 119 hours at 2 to 8°C
Freeze-thaw stability (cycles)	4 cycles at -60 to -80°C
Long-term storage stability (days)	254 days at -60 to -80°C for ceftaroline, ceftaroline fosamil, and ceftaroline ORM

* Adapted from Summary of the Analytical Method Reference (b) (4) 8307577

Plasma samples collected for Study P903-26 were analyzed within established stability. The assay performance is acceptable.

Pharmacokinetic Results

All patients (N=11) contributed at least 1 PK sample for a total of 19 plasma samples; 8 patients contributed 2 samples and 3 patients contributed 1 sample each. No CSF samples were collected from any patients in the study. Ceftaroline fosamil was measurable (>lower limit of quantification [LLOQ]) in only 3 samples while ceftaroline and ceftaroline M-1 (inactive metabolite) were measurable in all 19 samples. All these sparse plasma ceftaroline concentrations were included in the population PK analysis.

5.2.2. Population PK Analyses and Simulation Results

Population PK Analyses

Based on the original final population PK model of ceftaroline (CPT-MS-08 report submitted on 07 December 2015) which did not include PK samples from Study P903-26, for patients younger than 2 months of age, the covariates for their ceftaroline central compartment clearance (CLc) and central compartment volume of distribution (Vcc) are weight, age, and gestational age. As requested by the Agency, the Applicant updated the final population PK model by integrating PK samples from Study P903-26 and submitted it on 18 January 2019. The parameter estimates using the updated dataset are very similar to the final parameter estimates using the original CPT-MS-08 dataset without the additional data from Study P903-26.

Two studies (P903-21 and P903-26) in the ceftaroline development program included patients from birth to 2 months of age. In Study P903-21, twenty-three patients from birth to ≤28 days of age received a single dose of ceftaroline fosamil, but no patients were in the age range of >28 days to ≤2 months. In Study P903-26 (C2661002), eleven patients from birth to <2 months of age received multiple doses of ceftaroline fosamil. Among these eleven patients, seven patients were in the birth to ≤28 days age group and four were in the >28 days to <2 months age group. Therefore, when Studies P903-21 and P903-26 are combined together, a total of 30 patients are in the birth to ≤28 days age range and 4 patients are in the >28 days to ≤2 months range. The four patients in the >28 days to ≤2 months age group are term neonates. Please refer to Table 4 for the number of subjects in each age and gestational age group. From a clinical pharmacology perspective, the number of evaluable subjects in each age and gestational age group is acceptable for the dose recommendation of pediatric patients from birth to 2 months of age.

Table 4.[*]Number of Subjects in Studies P903-26 and P903-21 by Age and Gestational Age Group

Age	Gestational Age Group	Total	Study P903-26 (Multiple Dose)	Study P903-21[**] (Single Dose)
0 to ≤28 days	Preterm (≥34 to ≤37 weeks)	13	2	11[***]
0 to ≤28 days	Term (>37 weeks)	17	5	12
28 to 60 days	Term (>37 weeks)	4	4	0

[*]By the Clinical Pharmacology reviewer
[**]36 and 44 blood samples were collected with ceftaroline concentrations for preterm and term infants, respectively.
[***]Two neonate's gestational age was 33 weeks and one neonate's gestational age was 32 weeks.

Simulation Results

Simulations were conducted in subjects with normal renal function receiving a dose of 6 mg/kg ceftaroline fosamil every 8 hours by either a 5-minute or 1-hour IV infusion. The median steady-state ceftaroline PK exposures (C_{maxSS} and AUC_{24SS}) were compared to those of adult patients receiving a dose of 600 mg every 12 hours by IV infusion. The summary ratios are presented in

Table 5 (1-hour infusion) and Table 6 (5-minute infusion). Weights for the pediatric age groups were based on the CDC Growth Charts and Olsen et al.[7]

Table 5. Ratios for Median Steady State Ceftaroline C_{maxSS}, AUC_{24SS} by Age for Pediatric Patients With Normal Renal Function Following 6 mg/kg (Max of 400 mg) q8h Dosing (1 Hour Infusion) to the Exposure of Adult Doses of 600 mg q12h IV Infusion Given Over 1 Hour Based on Simulations

AGE	Weight (kg)	CmaxSS Ratios	AUC24SS Ratios
1-<2 months	4.69 (3.63,5.77)	0.670	1.07
0-<1 month	3.88 (2.91,4.75)	0.640	1.10
GA 38-<40 weeks	3.40 (2.55,4.24)	0.600	1.20
GA 36-<38 weeks	2.87 (2.07,3.75)	0.567	1.23
GA 34-<36 weeks	2.32 (1.71,3.05)	0.543	1.25
GA 32-<34 weeks	1.89 (1.38,2.44)	0.518	1.26
GA 30-<32 weeks	1.50 (1.05,1.95)	0.499	1.27
GA 28-<30 weeks	1.15 (0.779,1.52)	0.475	1.28

Abbreviations: C_{maxSS} = maximal concentration at steady state; AUC_{24SS} = area under the concentration-time curve from time 0 to 24 hours after drug administration at steady state; IV = intravenous
Source: Adapted from Table 2 in CPT-MS-08 Errata Report submitted on 3/7/2019

[7] Olsen, I.E., Groveman, S.A., Lawson, M.L., Clark, R.H. and Zemel, B.S. New intrauterine growth curves based on United States data. Pediatrics 125 (2010):e214–24.

Clinical Pharmacology Reviewer's Comments:

Based on the simulation data preparation code (preparesimcov.r.txt), postnatal age is 0 for simulated patients whose gestational age (GA) 28 to <40 weeks and GA is 40 weeks for all simulated patients age 0 to <2 months. This approach is acceptable.

Ratios are based on a summary of 100 simulated patients per month. Ratios are relative to the approved adult dosing regimen and represent the ratio of pediatric median to adult median for the adult dose of 600 mg q12h infusion over 60 minutes.

Table 6. Ratios for Median Steady State Ceftaroline C_{maxSS}, AUC_{24SS} by Age for Pediatric Patients With Normal Renal Function Following 6 mg/kg (Max of 400 mg) q8h Dosing (5 Minute Infusion) to the Exposure of Adult Doses of 600 mg q12h IV Infusion Given Over 5 Minutes Based on Simulations

AGE	Weight (kg)	CmaxSS Ratios	AUC24SS Ratios
1-<2 months	4.69 (3.63,5.77)	0.677	1.07
0-<1 month	3.88 (2.91,4.75)	0.620	1.10
GA 38-<40 weeks	3.40 (2.55,4.24)	0.551	1.20
GA 36-<38 weeks	2.87 (2.07,3.75)	0.505	1.23
GA 34-<36 weeks	2.32 (1.71,3.05)	0.479	1.25
GA 32-<34 weeks	1.89 (1.38,2.44)	0.447	1.26
GA 30-<32 weeks	1.50 (1.05,1.95)	0.416	1.28
GA 28-<30 weeks	1.15 (0.779,1.52)	0.396	1.28

Abbreviations: C_{maxSS} = maximal concentration at steady state; AUC_{24SS} = area under the concentration-time curve from time 0 to 24 hours after drug administration at steady state; IV = intravenous
Source: Adapted from Table 6 in CPT-MS-08 Errata Report submitted on 3/7/2019

According to the clinical pharmacology review by Dr. Aryun Kim for the original approval of ceftaroline in DARRTS dated 06 October 2010, the PK/PD index for ceftaroline is the percentage of the dosing interval with free drug concentrations that are greater than the minimum inhibitory concentration (%fT > MIC). This index was associated with in vivo efficacy in a neutropenic murine thigh model against *S. aureus*. For *S. aureus*, PK/PD targets included ≥26%, ≥36%, and ≥51% fT > MIC, median values respectively associated with net bacterial stasis, 1-log kill and 2-log kill against *S. aureus* isolates (n=4) in the neutropenic murine thigh model. Furthermore, susceptibility breakpoints have historically been dependent upon bacteriostatic targets for ABSSSI. The median percentage of simulated subjects who achieved %fT > MIC of ≥26% and 36% are summarized in Table 7 and 8, respectively. These tables are organized by MIC and age group for pediatric patients with normal renal function following a dose of 6 mg/kg (max of 400 mg) ceftaroline every 8 hours by 1-hour and 5 minutes IV infusion, respectively. According to the current ceftaroline label,[8] the susceptibility breakpoint for ceftaroline against *S. aureus* is 1 mg/L.

[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/200327s016s017lbl.pdf

Table 7. Median Percent of Subjects With ≥26% for %fT > MIC by Age for Normal Renal Function Following 6 mg/kg (Max of 400 mg) q8h Dosing (1-Hour or 5-Min Infusion) to Steady-State for Ceftaroline in Pediatric Patients Based on Simulations

Age	%26 (1 hr Infusion)*	26% (5 Minute Infusion)*
1≤2 months	100/100/100/100/100/71.3/1.67	100/100/100/100/99.7/63.0/1.00
0≤1 month	100/100/100/100/100/74.7/2.00	100/100/100/100/100/69.8/1.67
GA 38≤40 weeks	100/100/100/100/100/81.3/3.33	100/100/100/100/100/80.0/3.00
GA 36≤38 weeks	100/100/100/100/100/81.5/3.67	100/100/100/100/100/81.5/3.67
GA 34≤36 weeks	100/100/100/100/100/81.7/3.67	100/100/100/100/100/81.8/4.00
GA 32≤34 weeks	100/100/100/100/100/80.8/3.83	100/100/100/100/100/82.0/4.00
GA 30≤32 weeks	100/100/100/100/100/79.0/3.33	100/100/100/100/100/80.5/3.67
GA 28≤30 weeks	100/100/100/100/100/78.2/3.50	100/100/100/100/100/79.7/4.00

* Median based on summary of 100 trials. Medians displayed by MIC for MIC's of 0.125/0.25/0.5/1/2/4/8 mg/L.
Abbreviations: MIC = minimum inhibitory concentration
Source: Adapted from Tables 3 and 7 in CPT-MS-08 Errata Report submitted on 3/7/2019

Table 8. Median Percent of Subjects With ≥36% for %fT > MIC by Age for Normal Renal Function Following 6 mg/kg (Max of 400 mg) q8h Dosing (1 Hour or 5 Min Infusion) at Steady-State for Ceftaroline in Pediatric Patients Based on Simulations

Age	%36 (1 hr infusion)	36% (5 minute infusion)
1-<2 months	100/100/100/100/98.0/36.0/0.00	100/100/100/100/95.0/27.0/0.00
0-<1 month	100/100/100/100/99.0/42.8/0.333	100/100/100/100/97.7/35.3/0.00
GA 38-<40 weeks	100/100/100/100/99.7/57.0/0.667	100/100/100/100/99.5/51.5/0.667
GA 36-<38 weeks	100/100/100/100/100/61.0/1.00	100/100/100/100/99.7/57.8/1.00
GA 34-<36 weeks	100/100/100/100/100/63.5/1.33	100/100/100/100/100/60.5/1.00
GA 32-<34 weeks	100/100/100/100/100/65.0/1.33	100/100/100/100/100/64.2/1.33
GA 30-<32 weeks	100/100/100/100/100/65.8/1.33	100/100/100/100/100/65.5/1.17
GA 28-<30 weeks	100/100/100/100/100/67.3/1.67	100/100/100/100/100/66.7/1.67

Median based on summary of 100 trials. Medians displayed by MIC for MIC's of 0.125/0.25/0.5/1/2/4/8 mg/L.
Abbreviations: MIC = minimum inhibitory concentration; GA = gestational age
Source: Adapted from Tables 3 and 7 in CPT-MS-08 Errata Report submitted on 3/7/2019

Conclusions

- Because the gestational age for all preterm neonates in the multiple dose study (Study 903-26) and most (8/11) preterm neonates in the single dose study (Study 903-21) was ≥34 weeks, the recommended dose based on the population PK model and simulation should be only applied to neonates with a gestational age ≥34 weeks.
- Based on the simulation results, compared to adults with normal renal function receiving the approved dose of ceftaroline (i.e., 600 mg every 12 hours with 1 hr or 5 min infusion), pediatric patients from birth to <2 months of age with a gestational age ≥34 weeks receiving 6 mg/kg every 8 hours achieved higher AUC_{24SS} (up to 1.25 fold) and lower C_{maxSS} (down to 0.479 fold). Because the C_{maxSS} in pediatric patients (birth to 2 months) is lower compared to adult patients even with 5-minute infusion time, the proposed range of 30-60 minutes for the infusion time is acceptable from a Clinical Pharmacology perspective.

- The results of PK/PD target attainment analyses where the desired target is 26% and 36% for %fT > MIC associated with bacteriostasis and 1-log kill for *S. aureus* from neutropenic murine thigh models, respectively, support 1 µg/mL as the breakpoint for susceptibility in the current ceftaroline label in patients from birth to 2 months of age. The PTA analysis results also support the approval of the proposed dosing regimen, 6 mg/kg q8h, in patients age from birth to <2 months.

The duration of infusion in the two clinical studies for pediatric patients 0 to <2 months of age was 60 minutes. No patient in this age group received a 5-minute infusion. Based on the current ceftaroline label,[9] Teflaro is supplied as 600 mg or 400 mg of sterile ceftaroline fosamil powder in single-dose, 20 mL clear glass vials. The powder is first constituted with 20 mL Sterile Water for Injection USP; or 0.9% of sodium chloride injection (normal saline); or 5% of dextrose injection; or lactated ringer's injection and then further diluted in a range between 50 mL to 250 mL before intravenous infusion into patients. The final concentration of ceftaroline fosamil is approximately 12 mg/mL and 8 mg/mL, respectively, when diluting 600 mg and 400 mg constituted solution into a 50 mL infusion bag. Therefore, for a 3-kg neonate, the total infusion volume is 1.5 mL and 2.25 mL for 12 mg/mL and 8 mg/mL solution, respectively. The final concentration of ceftaroline fosamil is approximately 2.4 mg/mL and 1.6 mg/mL, respectively, when diluting 600 mg and 400 mg constituted solution into 250 mL infusion bag. Consequently, for a 3-kg neonate, the total infusion volume is 7.5 mL and 11.25 mL, respectively, for 2.4 mg/mL and 1.6 mg/mL solution.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

This sNDA includes data from two clinical trials, as summarized in Table 9.

Study P903-26 was an open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline in neonates and young infants with late-onset sepsis. Study P903-26 was initiated in April 2014 and completed in December 2017.

Study P903-21 was an open-label, sequential, single-dose, prospective PK study in pediatric patients from birth to younger than 12 years of age with suspected or confirmed infection. This study provides supportive neonatal pharmacokinetic data for the current sNDA. Study P903-21 was initiated in April 2011 and completed in February 2013.

Please see Section 3 for additional details.

[9] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/200327s016s017lbl.pdf

Table 9. Listing of Clinical Trials Relevant to NDA 200327 S-22

Trial Identity/ ClinicalTrials.gov Identifier/ Study Title	Trial Design	Study Population (Number Enrolled)	Study Endpoint	Study Treatment	Treatment Duration/ Follow-up	Country and Number of Sites
P903-26 Also known as D3720C00009 (C2661002) due to Applicant changes. NCT02424734 Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline in Neonates and Young Infants with Late-Onset Sepsis.	Open-label, single-arm study with no randomization.	Total patients enrolled: 11 **Cohort 1**: Young infants (postnatal age >28 days to <60 days): n=4, **Cohort 2**: Term neonates (gestational age ≥37 weeks and postnatal age 7 to ≤28 days): n=5, **Cohort 3**: Preterm neonates (gestational age ≥34 weeks to <37 weeks and postnatal age 7 to ≤28 days): n=2.	No primary efficacy evaluation. *Secondary efficacy outcome measures:* Clinical response and microbiological response (per-patient and per-pathogen) at End-of-Therapy (EOT) and Test-of-Cure (TOC).	IV ceftaroline fosamil and ampicillin, *plus* an optional aminoglycoside of choice as an empiric therapy for late-onset sepsis. *Protocol amendment 2:* Ceftaroline fosamil 6 mg/kg as a 60-minute (±10 min) infusion q8h (±1 hour) (n=8). *Prior to protocol amendment 2:* Ceftaroline fosamil 4 mg/kg as a 60-minute (±10 min) infusion every 8 hours (q8h) (±1 hour) (n=3).	Treatment duration: 48 hours (minimum) to 14 days (maximum). Study duration: up to 49 days. Follow-up: Safety follow-up visit occurred 21 to 35 days after the last dose of study treatment.	Hungary: 3 United States: 1

Trial Identity/ ClinicalTrials.gov Identifier/ Study Title	Trial Design	Study Population (Number Enrolled)	Study Endpoint	Study Treatment	Treatment Duration/ Follow-up	Country and Number of Sites
P903-21 NCT01298843 Pharmacokinetics of a Single Dose of Ceftaroline fosamil in Children Ages Birth to Younger Than 12 Years With Suspected or Confirmed Infection.	Open-label, sequential, single-dose, prospective PK study.	Total patients enrolled: **Cohort 1**: children, ≥6 to <12 years (n=10) **Cohort 2**: children, ≥2 to <6 years (n=8) **Cohort 3***: young infants and toddlers, ≥28 days to <2 years (n=12) **Cohort 4**: Full-term neonates (gestational age ≥37 weeks and postnatal age <28 days) (n=12) **Cohort 5**: Preterm neonates (gestational age 35 to 37 weeks and postnatal age <28 days) (n=11)	No primary efficacy evaluation. Single-dose PK profile, safety, and tolerability.	IV ceftaroline fosamil **Cohort 1**: 10 mg/kg (max dose of 600 mg for body weight ≥60 kg) as a 1-hr infusion **Cohort 2**: 15 mg/kg as a 1.5-hr infusion **Cohort 3**: 12 mg/kg as a 1-hr infusion for age ≥5 months and 8 mg/kg as a 1-hr infusion for age 28 days to 5 months **Cohorts 4 and 5**: 8 mg/kg as a 1-hr infusion	Treatment duration: 1-hr infusion. Study duration: up to 5 days. Follow-up: Day 1 through follow-up on Day 4 [±1 day].	United States: 12

*No young infants (postnatal age >28 days to <60 days) were enrolled in Cohort 3.
Abbreviations: PK = pharmacokinetics; IV = intravenous

6.2. Review Strategy

The safety review included an analysis of data from all 11 patients enrolled in Study P903-26.

7 Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. Study P903-26: Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline in Neonates and Young Infants With Late-Onset Sepsis

Trial Design

Study P903-26 was an open-label, single-arm study with no randomization. The study was intended to be conducted in approximately 30 centers worldwide.

The Applicant had planned to enroll at least 24 patients with late-onset sepsis (LOS) within 3 age cohorts of 8 patients each:

- Young infants (postnatal age >28 days to <60 days)
- Term neonates (gestational age ≥37 weeks and postnatal age 7 to ≤28 days)
- Preterm neonates (gestational age ≥34 weeks to <37 weeks and postnatal age 7 to ≤28 days)

Patients were required to be diagnosed with sepsis within 36 hours before enrollment, defined as the presence of at least 2 clinical criteria and at least 1 laboratory criterion in the presence of, or as a result of, suspected or proven bacterial infection that required IV antibacterial drug therapy. Prior to protocol amendment 3, the presence of at least two laboratory criteria were required.

Clinical criteria included the following (at least 2 required for enrollment):

- Hypothermia (<36°C) **or** fever (>38.5°C)
- Bradycardia **or** tachycardia **or** rhythm instability
- Urine output 0.5 to 1 mL/kg/h **or** hypotension **or** mottled skin **or** impaired peripheral perfusion
- Petechial rash **or** sclerema neonatorum
- New onset or worsening of apnea episodes **or** tachypnea episodes **or** increased oxygen requirements **or** requirement for ventilation support

- Feeding intolerance **or** poor sucking **or** abdominal distension
- Irritability
- Lethargy
- Hypotonia

Laboratory criteria included the following (at least 1 required for enrollment; prior to protocol amendment 3, at least 2 required for enrollment):

- White blood cell count ≤4.0 × 10^9/L **or** ≥20.0 × 10^9/L
- Immature to total neutrophil ratio >0.2
- Platelet count ≥100 × 10^9/L
- C-reactive protein (CRP) >15 mg/L **or** procalcitonin ≥2 ng/mL
- Hyperglycemia **or** hypoglycemia
- Metabolic acidosis

Enrolled patients received a combination of intravenous (IV) ceftaroline fosamil and ampicillin, plus an optional aminoglycoside of choice as empiric therapy for LOS. Study patients received ceftaroline fosamil at a dose of 6 mg/kg IV over 60 (±10) minutes q8h (±1 hour). Patients enrolled prior to amendment 2 received ceftaroline fosamil at a dose of 4 mg/kg over 60 [±10] minutes q8h [±1 hour].

The use of IV ampicillin for the first 48 hours was mandatory if the presence of an organism that required treatment with ampicillin could not be excluded. If the results of additional microbiology, polymerase chain reaction, or other investigations indicated that ampicillin during the first 48 hours of treatment was not required, then ampicillin use was at the Investigator's discretion.

Patients participated in the study for up to 49 days. The duration of study therapy was from 48 hours (minimum) up to 14 days (maximum). Hospitalization was required during IV study therapy. Baseline assessments for study eligibility occurred within 36 hours before the first dose of study therapy. The safety follow-up assessments occurred 21 to 35 days after the last dose of study therapy.

Safety assessments were done throughout the study. Blood and urine samples were collected at Baseline and EOT. Study P903-26 Laboratory Safety Variables). Between Days 2 and 14, two blood samples were collected for PK analysis. The efficacy of ceftaroline was evaluated based on the clinical outcome (clinical cure, clinical failure, or intermediate) at end-of-therapy (EOT) and test-of-cure (TOC) assessments.

Study Endpoints

The primary objective of Study P903-26 was to evaluate the safety of ceftaroline for the treatment of late-onset sepsis in neonates and young infants 7 to <60 postnatal days of age.

Secondary objectives included the evaluation of the PK profile and efficacy of ceftaroline for the treatment of late-onset sepsis in neonates and young infants 7 to <60 postnatal days of age.

Clinical outcome categories and per-pathogen microbiological outcome categories at end-of-therapy (EOT) and test-of-cure (TOC) used in Study P903-26 are summarized in Table 10 and Table 11.

Table 10. Clinical Outcome Categories

Outcome	Definition	EOT or TOC
Clinical Cure	Resolution of all acute signs and symptoms of LOS or improvement to such an extent that no further antibacterial therapy was required.	EOT and TOC
Clinical Failure	Patients who received ≥ 48 hours of study drug and met any of the following criteria:	
	• Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, worsening in signs and symptoms of LOS or isolation of a resistant pathogen that required alternative non-study antibacterial therapy.	EOT
	• Discontinuation of study drug due to a study drug-related AE and requirement for alternative non-study antibacterial therapy for LOS.	EOT
	• Incomplete resolution or worsening of LOS signs or symptoms of development of new signs or symptoms, or isolation of a resistant pathogen requiring alternative nonstudy antibacterial therapy.	TOC
	• Death in which LOS was contributory.	EOT and TOC
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including:	
	• Death in which LOS was clearly noncontributory	EOT and TOC
	• LTFU	EOT and TOC
	• Extenuating circumstances precluding classification as a cure or failure	EOT and TOC
	• Diagnosis of CNS infection, osteomyelitis, endocarditis, or NEC at any time after enrollment.	EOT and TOC
	• Received < 48 hours of study drug.	EOT and TOC

Abbreviations: CNS = central nervous system; EOT = end of treatment; LTFU = lost to follow-up; TOC = test of cure
Source: NDA 200327 SD636 Module 2.5 Clinical Overview, Table 5-1.

Table 11. Per-Pathogen Microbiological Outcome Categories at EOT and TOC

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

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

Source: NDA 200327 SD636 Module 2.5 Clinical Overview, Table 5-2.

Statistical Analysis Plan

A statistical analysis plan was available for this study and documented how data were to be summarized. As the primary objective was to evaluate safety and tolerability, the sample size was not chosen to test any formal statistical hypotheses. The statistical analysis plan specified that results were to be presented descriptively, and to be presented within age cohorts.

There was no primary efficacy analysis, but efficacy outcomes were to be analyzed using the following analysis populations:

- Intent-to-Treat (ITT): All patients.
- Microbiological ITT (Micro-ITT): Patients who had one or more potentially causative baseline pathogen identified.
- Modified Intent-to-Treat (mITT): Patients who received any amount of ceftaroline fosamil and met minimal disease criteria of late-onset sepsis (excluding patients with confirmed infection with a pathogen known to be resistant to ceftaroline fosamil, or confirmed fungal, parasitic, or viral pathogen as the sole cause of infection).

Protocol Amendments

Protocol amendments for Study P903-26 are summarized in Table 12.

Table 12. Study P903-26 Summary of Protocol Amendments

P903-26 PROTOCOL AMENDMENTS						
Amendment No.	**Original (Edition 0)**	**Original (Edition 1)**	**Amendment 1 (Edition 2)**	**Amendment 2 (Edition 3)**	**Amendment 3 (Version 4)**	**Amendment 4 (Version 5)**
IND Submission Date	30-May-14	24-Dec-14	30-Jun-15	8-Jan-16	7-Sep-16	17-Jul-17
IND Sequence No.	506	519	524	531	535	542
Implementation Date	01-Jun-14	02-Feb-2015	04-Aug-2015	4-Feb-16	17-Sept-16	18-Jul-17
Patients Enrolled	0	0	3	5	10	11
Summary of Changes	Initial creation	There were no major changes to the content of the study protocol; wording was adjusted to match the AstraZeneca template only when necessary.	The definition of preterm neonate was revised in order to align with the World Health Organization definition of preterm neonates used world-wide. The discrepancy between units and values for white blood cell and platelet counts in the inclusion criteria was corrected. The definition of Study Day was clarified – Study Days were to be calculated starting from the onset of the first dose of study therapy, in 24-hour increments. In addition, some minor typographic errors were corrected.	AstraZeneca representative was added as a signatory to the revised protocol. Clarification was provided for when ampicillin administration is mandatory. The dose of ceftaroline fosamil to be given was increased to 6 mg/kg. The estimated date for last patient completed and study end were updated to align with the Pediatric Investigation Plan for ceftaroline fosamil. Minor wording changes were added to the text as clarifications.	Revised to the latest AstraZeneca designated template. Date of pediatric approval in the US (May 2016) and EU (June 2016) was added. Inclusion criterion 5 was revised so that patients must meet at least 1 of the listed laboratory criteria, rather than 2 of the criteria. Following a request from the Italian Ministry of Health, a justification was provided for the dose increase to 6 mg/kg that was described in Edition 3 of the protocol. Clarification was added to the effect that the individual dose of Ceftaroline fosamil should be calculated based on the patient's first weight of the day.	Revised to indicate the change in study sponsorship and to include Pfizer's current protocol template language. The visit window for the Safety Follow Up (SFU) assessment was also changed to 28 days from 35 days to be consistent with Pfizer's requirement to follow safety for a minimum of 28 days after the last dose of study therapy. Minor text changes were made to improve protocol clarity.

IND = Investigational New Drug
Source: NDA 200327 SD636 Module 1.2 Reviewer's Guide, Table 7-1.

7.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant stated that the study was conducted in compliance with Good Clinical Practice guidelines.

Financial Disclosure

Financial certifications and disclosures are provided in Module 1.3.4. Please see Section 14.2 Financial Disclosure for additional information.

Data Quality and Integrity

Data quality and integrity were considered sufficient for review purposes.

Clinical Datasets

The dataset package for Study P903-26 was submitted in accordance with FDA Study Data Technical Conformance Guide.

Patient Disposition

There were a total of 11 patients: 4 young infants, 5 term neonates, and 2 preterm neonates. All patients in the study received treatment, but 4 of the 11 patients discontinued treatment early because they improved and were discharged home.

Of the 11 patients in the study, all were included in the ITT analysis set (by definition). There were three patients excluded from the MITT analysis set due to *E. coli* or *E. faecalis* resistant to ceftaroline. Only one patient was excluded from the Micro-ITT analysis set, due to no baseline microbiology data.

Protocol Violations/Deviations

All 11 patients experienced at least 1 protocol deviation. The most common deviation was that five patients had "lab not done." In addition, four patients had antibacterial drug switch deviations, and they were all enrolled at the same study site in the United States. Incorrect dose rounding was used for two patients.

Table of Demographic Characteristics

There were 4 young infants (aged >28 days to <60 days), 5 term neonates (aged 7 to ≤28 days, gestational age ≥37 weeks), and 2 preterm neonates (aged 7 to ≤28 days, gestational age ≥34 to <37 weeks). Of the 11 patients, 6 were male and 5 were female. One patient was Asian, and the remaining 10 patients were white.

The study was conducted in the United States (1 site) and Hungary (3 sites): 4 of the 11 patients were enrolled at a single study site in the United States, and 7 patients were enrolled at 3 Hungarian sites.

Other Baseline Characteristics

Table 13 summarizes baseline pathogens and specimen types for patients in the study. The most common pathogen was *E. coli*, which was identified in 1 blood sample, 5 urine samples, and 3 other samples.

Table 13. Summary of Baseline Pathogens (Micro-ITT Analysis Set)

Specimen Type	Baseline Pathogen	Cohort 1 (N = 3)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 10)
Blood	*Enterobacter aerogenes*	1	0	0	1
	Escherichia coli	0	1	0	1
	Staphylococcus epidermidis	0	0	1	1
	Staphylococcus hominis	1	0	0	1
	Streptococcus salivarius group	0	1	1	2
Urine	*Enterobacter aerogenes*	1	0	0	1
	Enterococcus faecalis	0	1	1	2
	Escherichia coli	2	3	0	5
	Klebsiella pneumoniae	0	0	1	1
	Streptococcus agalactiae	0	1	0	1
Other	*Escherichia coli*	0	2	1	3
	Staphylococcus aureus	1	1	1	3

Source: Table 14.1.2.1.5.2
Cohort 1, 1 patient had other - sputum/nose as specimen type. Cohort 2, 2 patients had other - sputum/throat and 1 patient had other - sputum/throat tissue as specimen type. Cohort 3, 1 patient had other - other/nose (*E. coli*) and other - other/throat (*S. aureus*) as specimen types.
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
ITT = Intent-to-Treat; n = Number of pathogens, patients could have multiple pathogens at baseline;
N = number of patients in the cohort.
Source: NDA 200327 SD636 Study P903-26 (Protocol D3720C00009 [C2661002]), Full Clinical Study Report, Table 13.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

For each subject in the study, ceftaroline compliance was calculated as 100*(actual infusions/expected infusions). By this measure, all 11 subjects had between 80% and 120% compliance.

Efficacy Results

There was no primary efficacy outcome. However, the Applicant provided descriptive summaries for clinical and microbiological responses. There were no clinical failures in the study. Of the 11 patients in the study, 7/11 (63.6%) were classified as having clinical cure at the

EOT and TOC visits. The remaining four patients had indeterminate outcomes, because they were prematurely discharged from the hospital.

M.O. Comment: *All 11 subjects in the study could reasonably be considered to have had successful clinical outcomes. Concomitant antibacterial drugs included ampicillin, ceftazidime, cefotaxime and gentamicin.*

A favorable microbiologic response was defined as eradication or presumed eradication of the baseline pathogen. Of the 10 patients with positive baseline cultures, 5/10 (50%) had a favorable response at the TOC visit. All of the favorable responses at the TOC visit were due to presumed eradication rather than documented eradication. Of the five patients without favorable responses, 3 were previously discussed patients who were prematurely discharged from the hospital, and were classified as having indeterminate microbiological outcomes. One patient with an unfavorable microbiological response at the TOC visit had baseline *E. coli* in the urine that was not susceptible to ceftaroline (MIC >32 mg/L), a positive sputum culture for *E. coli* obtained at the TOC, and no follow-up urine culture available at the TOC. A second patient with an unfavorable microbiological response had ceftaroline-susceptible, ESBL-negative, baseline *E. coli* in the urine that was persistent at the TOC visit. Both of these patients with unfavorable microbiological outcomes were classified as having clinical cure at the EOT and TOC visits.

7.1.3. Integrated Assessment of Effectiveness

Assessment of efficacy was limited by small sample size of 11 patients, lack of a control group, and descriptive analysis. Nevertheless, results did not point to any particular efficacy concern, as all patients were either classified as having clinical cure at the EOT and TOC visits or prematurely discharged due to improvement.

7.2. Review of Safety

7.2.1. Safety Review Approach

The safety review included analysis of the 11 subjects enrolled in Study P903-26.

7.2.2. Review of the Safety Database

Overall Exposure

In the Safety Analysis Set, all 11 patients were exposed to ceftaroline, and the mean duration of ceftaroline exposure was 8.5±3.53 days (median 8.0 days, range 3 to 15 days). The mean duration of ceftaroline exposure in the individual cohorts was similar.

M.O. Comment: *As noted by the Clinical Pharmacology reviewer, all 11 subjects received ceftaroline infusions over 60 minutes. The Applicant proposed a* (b) (4) *minute infusion time in the label for pediatric patients 0 to <2 months of age. The Division noted that* (b) (4) *. The Applicant then requested an infusion time range of 30-60 minutes. This proposal was found to be acceptable* (b) (4)

As per the protocol, ampicillin treatment was initiated at baseline and continued for a minimum of 48 hours. After 48 hours, the duration of treatment with ampicillin was at the discretion of the Investigator. Nine of the 11 patients in the study received ampicillin and the mean duration of exposure was 4.8±2.86 days (median 3.0, range 2 to 11 days).

Per the protocol, aminoglycoside use was optional from baseline through the entire study. Six patients received aminoglycosides and the mean duration of exposure was 7.7±3.78 days (median 7.5, range 3 to 12 days).

Adequacy of the Safety Database

The Safety Analysis Set consisted of 11 patients with late-onset sepsis, with the majority receiving concomitant antibacterial drug treatment. Due to the relatively small database, conclusions regarding safety in this pediatric population are limited.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Please see Section 7.1.2 Study Results – Clinical Datasets.

Categorization of Adverse Events

The Applicant used Medical Dictionary for Regulatory Activities (MedDRA, v20.0) coding for mapping investigator verbatim terms to preferred terms.

7.2.4. Safety Results

Overview

An overview of treatment-emergent adverse events in any category are summarized in Table 14.

Table 14. Treatment-Emergent Adverse Events in Any Category – Safety Analysis Set

	Number (%) of Patients[a]			
AE Category	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Any AE	1 (25.0)	3 (60.0)	1 (50.0)	5 (45.5)
Any AE causally related to ceftaroline fosamil[b]	0	1 (20.0)	0	1 (9.1)
Any SAE (including events with outcome = death)	0	0	1 (50.0)	1 (9.1)
Any AE of severe intensity	0	0	1 (50.0)	1 (9.1)

Source: Table 14.3.1.1
Includes adverse events with an onset date between the date of first dose and Safety Follow-up assessment.
Percentages are based on the total number of patients in the cohort (N).
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
AE = adverse event; N = number of patients in each age cohort and overall; SAE = serious adverse event.
a. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
b. As assessed by the Investigator.
Source: NDA 200327 SD636 Study P903-26 Clinical Study Report, Table 22.

Deaths

There were no deaths among enrolled patients.

Serious Adverse Events

One serious adverse event (SAE), salmonellosis, was reported for 1 (9.1%) patient in Cohort 3 (Subject (b) (6)). The SAE started on Day 29 (21 days after last dose of ceftaroline), was severe, resolved and was considered unrelated to study treatment.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no adverse events (AEs) leading to dose reduction, temporary discontinuation or complete discontinuation of ceftaroline treatment.

Significant Adverse Events

There was one AE which the Investigator determined was related to study drug, diarrhea. This AE was experienced by a subject in Cohort 2. The event was mild in severity and resolved.

M.O. Comment: *Diarrhea is a known adverse reaction associated with ceftaroline use in adult and older pediatric patients.*

Treatment-Emergent Adverse Events and Adverse Reactions

Five (45.5%) patients in the Safety Analysis Set experienced a total of 10 AEs (Table 15). All except one AE were reported as mild, and nonserious, and resolved with or without treatment.

Table 15. Treatment-Emergent Adverse Events, by System Organ Class and Preferred Term - Safety Analysis Set

System Organ Class Preferred Term	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
	Number (%) of Patients[a]			
Patients with any AE	1 (25.0)	3 (60.0)	1 (50.0)	5 (45.5)
Infections and infestations	0	1 (20.0)	1 (50.0)	2 (18.2)
Oral candidiasis	0	1 (20.0)	0	1 (9.1)
Otitis externa	0	0	1 (50.0)	1 (9.1)
Rhinitis	0	0	1 (50.0)	1 (9.1)
Salmonellosis	0	0	1 (50.0)	1 (9.1)
Blood and lymphatic system disorders	0	0	1 (50.0)	1 (9.1)
Anaemia	0	0	1 (50.0)	1 (9.1)
Nervous system disorders	0	1 (20.0)	0	1 (9.1)
Cerebral cyst	0	1 (20.0)	0	1 (9.1)
	Number (%) of Patients[a]			
System Organ Class Preferred Term	Cohort 1 (N = 4)	Cohort 2 (N = 5)	Cohort 3 (N = 2)	Total (N = 11)
Gastrointestinal disorders	1 (25.0)	1 (20.0)	0	2 (18.2)
Diarrhoea	1 (25.0)	1 (20.0)	0	2 (18.2)
Skin and subcutaneous tissue disorders	0	1 (20.0)	0	1 (9.1)
Dermatitis	0	1 (20.0)	0	1 (9.1)
Renal and urinary disorders	1 (25.0)	0	0	1 (9.1)
Pyelocaliectasis	1 (25.0)	0	0	1 (9.1)

Source: Table 14.3.1.3
A patient can have 1 or more PTs reported under a given SOC. Includes AEs with an onset date between the date of first dose and Safety Follow-up assessment.
MedDRA version 20.0 applied.
Percentages are based on the total number of patients in the cohort (N).
Cohort 1 = Young infants, Cohort 2 = Term neonates, Cohort 3 = Preterm neonates.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in each age cohort and overall; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
a. Number (%) of patients with AEs, sorted by SOC in international order and by PT in decreasing order of frequency in the total column.

Source: NDA 200327 SD636 Study P903-26 Clinical Study Report, Table 23.

Laboratory Findings

Potentially Clinically Significant Laboratory Values

One patient experienced anemia in Cohort 3 (Male, aged 19 days, Subject (b) (6)) at TOC (Day 19). The hematocrit (ratio) dropped to 0.237 from a Baseline (Day -2) value of 0.360. The anemia was considered mild in severity, and deemed unrelated to study treatment. The AE outcome was reported as recovering/resolving by the end of the study.

Cerebrospinal Fluid

In Study P903-26, four patients ((b) (6)) of the 11 total had baseline CSF samples obtained, which were negative for bacterial pathogens by Gram stain or culture, when results were available (Study P903-26, Clinical Study Report, Table 16.2.6.8.1). No patient had CSF samples obtained while on ceftaroline treatment.

Vital Signs

No clinically significant safety observations related to vitals signs were noted.

7.2.5. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups were not conducted due to the small sample size and homogeneous study population demographics. The majority of subjects were white (10/11, 91%), male (6/11, 55%), and not hispanic or Latino (10/11, 91%).

7.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Important Risks

Ceftaroline is a cephalosporin and shares risks associated with the β-lactam class of antibacterial drugs. Identified and potential risks associated with ceftaroline use are summarized in Table 16.

Table 16. Important Reported Risks Associated With Ceftaroline

Important identified risks	*Clostridium difficile*-associated diarrhea[a]
	Hypersensitivity/anaphylaxis[a]
Important potential risks	Bacterial resistance development
	Convulsions/seizures
	Drug-induced liver injury
	Haemolytic anaemia
	Renal impairment (including potential drug interactions with nephrotoxic agents)
	Potential for off-label use

[a] Reclassified as not important identified risks as per the EU RMP version 16, dated March 2018. This will no longer be listed in the next DSUR.

Source: IND 071371 SD543 DSUR Table 18-1.

Development Safety Update Report

The Development Safety Update Report (DSUR), for the reporting period 29 October 2017 to 28 October 2018, was reviewed under IND 071371 (SD543, submitted 11 December 2018). As of 28 October 2018, ceftaroline was approved in 72 countries. During the period covered by this report no actions related to ceftaroline were taken by Allergan or Pfizer or by a regulatory authority for safety reasons.

Periodic Adverse Drug Experience Report

The Periodic Adverse Drug Experience Report (PADER) for the reporting period 29 October 2017 to 28 October 2018 was reviewed under NDA 200327 (SD637, submitted 20 November 2018).

There was a total of 85 Adverse Drug Experience Reports, 72 of which were 15-day Alert Reports, and 13 of which were Non-15-day Reports. There were a total of 166 adverse events reported, including 92 serious and 74 nonserious adverse events.

No changes to labeling were made during the reporting period.

There were three Serious Listed Reports. All were for neutropenia. Neutropenia is listed as an adverse reaction in the approved ceftaroline label.

Of note, eosinophilic pneumonia was identified in the Serious Unlisted Reports. In addition to cases noted in this PADER, there are cases of eosinophilic pneumonia associated with ceftaroline exposure reported in the literature.[10,11,12,13] The cases from the literature presented with dyspnea, respiratory decompensation, hypoxemia, pulmonary infiltrates on chest imaging,

[10] Desai KR, et al. Ceftaroline-induced eosinophilic pneumonia. Pharmacotherapy 2013; 33(7): e166-e9.
[11] Griffiths CL, et al. Eosinophilic pneumonia induced by ceftaroline. Am J Health Syst Pharm 2014; 71(5): 403-6.
[12] Polenakovik HM, Pleiman CM. Ceftaroline for meticillin-resistant Staphylococcus aureus bacteraemia: case series and review of the literature. Int J Antimicrob Agents 2013; 42(5): 450-5.
[13] Watkins RR, et al. DISC: Describing Infections of the Spine treated with Ceftaroline. J Glob Antimicrob Resist 2018; 13: 146-51.

peripheral eosinophilia, and bronchoalveolar lavage fluid demonstating the presence of pulmonary eosinophilia. The literature reports noted that eosinophilic pneumonia resolved with ceftaroline de-challenge and use of steroids. The cases do not appear to be dose or duration dependent.

In the reported cases, causality in the association between ceftaroline and eosinophilic pneumonia could not be excluded.

M.O. Comment: *The Applicant agreed to the inclusion of eosinophilic pneumonia in Section 6.2, Postmarketing Experience of the label.*

7.2.7. Integrated Assessment of Safety

Study P903-26 enrolled 11 patients with late-onset sepsis. The ability to assess safety with ceftaroline exposure for the preterm neonate, term neonate, and young infant population, is limited based on the small safety database submitted. There were no deaths, no adverse events that led to discontinuation from treatment or from the study, and no adverse events of special interest reported. The majority of adverse events reported were mild, and nonserious. There was one subject with a serious adverse event of salmonellosis which appeared unrelated to ceftaroline. One subject experienced anemia as an adverse event, mild in severity. Anemia is a labeled adverse reaction in section 6 of the current label. In the postmarket setting, eosinophilic pneumonia is a risk associated with ceftaroline use and is incorporated in Section 6.2 of labeling.

7.3. Statistical Issues

Nontrivial statistical issues did not arise in this submission due to the small sample size, lack of control group, and descriptive summaries provided for Study P903-26.

7.4. Conclusions and Recommendations

The safety and effectiveness of Teflaro were evaluated in a single study that enrolled 11 pediatric patients with a gestational age of ≥34 weeks and a postnatal age of 12 days to less than 2 months of age with known or suspected infections. The majority of patients (8 of 11) received 6 mg/kg Teflaro every 8 hours as an intravenous (IV) infusion over 60 minutes. A finding of efficacy for this pediatric population is based on extrapolation from adult and older pediatric patients (≥2 months of age) and pharmacokinetic model-based analyses demonstrating similar ceftaroline exposure in adults and the proposed pediatric population down to 34 weeks gestational age and 12 days postnatal age, using a dose of 6 mg/kg as a 30-60 minute infusion every 8 hours. Safety findings in these 11 pediatric patients were limited, but similar to those observed in adult and pediatric patients 2 months of age and older.

8 Pediatrics

As noted previously in the review, ceftaroline fosamil is indicated in adult and pediatric patients 2 months of age and older for the treatment of ABSSSI and CABP caused by susceptible isolates of selected bacterial pathogens.

This sNDA addresses PMR 1692-005, ceftaroline fosamil use in pediatric patients less than 2 months of age for the currently approved indications (ABSSSI and CABP).

The Division discussed the information provided in the sNDA with PeRC on May 1, 2019. PeRC agreed that if the Division labeled ceftaroline for ABSSSI, then PMR 1692-005 could be considered fulfilled, and concurred with the Division's assessment that due to the differences in the etiology and pathophysiology of CABP in pediatric patients less than 2 months of age, efficacy findings from CABP studies could be extrapolated to infants less than 2 months of age. PeRC encouraged labeling ceftaroline for ABSSSI in pediatric patients less than 2 months of age even with the limited safety information provided in the sNDA.

9 Advisory Committee Meeting and Other External Consultations

As there were no specific issues that needed external input, no advisory committee meeting or external consultations were held.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

10.1.1. Prescribing Information

A high-level summary of significant labeling changes are summarized in the following table.

Table 17. High-Level Summary of Labeling Changes

Section of Label	Applicant Proposed Labeling	Approved Labeling
Highlights	No changes.	As noted below, updates to Indications and Usage and Dosage and Administration.
1. Indications and Usage	No changes. Did not propose to change indication statement to include pediatric patients <2 months of age.	Under Section 1.1, ABSSSI indication extended to include treatment of pediatric patients at least 34 weeks gestational age and 12 days postnatal age.

Section of Label	Applicant Proposed Labeling	Approved Labeling
2. Dosage and Administration	No changes.	Included section on pediatric patients less than 2 months of age. Noted that concentrations of Teflaro in the CSF have not been obtained, and that there is no dosing information in infants less than 34 weeks gestational age and less than 12 days postnatal age.
6. Adverse Reactions	No changes.	Addition of eosinophilic pneumonia to Section 6.2 Postmarketing Experience.
8.4 Pediatric Use	(b) (4)	Revisions to note that use of Teflaro in pediatric patients less than 2 months of age was supported by pharmacokinetic and safety data in 11 infants at least 34 weeks gestational age and 12 days postnatal age. In these infants, noted that concentrations of Teflaro in the CSF were not evaluated. Deletion of (b) (4).
12 Clinical Pharmacology	No changes.	Added that no clinically significant differences in ceftaroline AUC were predicted in patients from 12 days to 2 months postnatal age and with ≥34 weeks of gestational age compared to adults and pediatric patients 2 months of age and older when given the approved recommended dosage for each patient population.
13 Nonclinical Toxicology	No changes.	
14 Clinical Studies	No changes.	Added that the safety and effectiveness of Teflaro were evaluated in a single study that enrolled 11 pediatric patients with a gestational age of ≥34 weeks and a postnatal age of 12 days to less than 2 months of age with known or suspected infections, and that the majority of patients (8 of 11) received 6 mg/kg Teflaro every 8 hours as an intravenous (IV) infusion over 60 minutes.

10.1.2. Other Prescription Drug Labeling

No other prescription drug labeling is applicable to this submission.

11 Risk Evaluation and Mitigation Strategies (REMS)

No REMS were issued for this application.

12 Postmarketing Requirements and Commitment

Please see Section 3 Regulatory Background for details regarding PMR 1692-005.

The Applicant can be released from PMR 1692-005. There are no additional PMRs.

13 Division Director (DAIP) Comments

I concur with the review team's assessment and recommendations.

14 Appendices

14.1. References

References are included as footnotes throughout the review.

14.2. Financial Disclosure

Covered Clinical Study: Study P903-26 (D3720C00009): Open-label, Multicentre Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline in Neonates and Young Infants with Late-Onset Sepsis.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 16		
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: *Not applicable.* Significant payments of other sorts: *Not applicable.* Proprietary interest in the product tested held by investigator: *Not applicable.* Significant equity interest held by investigator in S Sponsor of covered study: *Not applicable.*		
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) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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