CLINICAL PHARMACOLOGY REVIEW

NDA#	NDA 200327/S-16 and S-17
Product	Teflaro® (ceftaroline fosamil) IV infusion
Submission Date(s)	12/7/2015
Submission Type	Supplemental NDA, pediatric studies
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1. Executive Summary

Ceftaroline fosamil is the water-soluble prodrug of the bioactive ceftaroline. Ceftaroline fosamil is converted to bioactive ceftaroline in plasma by a phosphatase enzyme. Ceftaroline fosamil (Teflaro®) was approved by the FDA on 10/29/2010 in adults for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) caused by isolates including both methicillin-susceptible *S. aureus* (MSSA) (b) (4) and Community Acquired Bacterial Pneumonia (CABP).

The recommended dosage of ceftaroline fosamil in adult patients with normal renal function is 600 mg administered every 12 hours by intravenous (IV) infusion. The duration of therapy ranges between 5 to 14 days (5 to 14 days for ABSSSI and 5 to 7 days for CABP) and should be guided by disease severity, site of infection, and patient's clinical and bacteriological progress. The original approved duration of infusion for ceftaroline fosamil was one hour, and was revised to a range of 5 minutes to 1 hour in adults with the approval of Supplement 14 on 8/31/2015.

The purpose of these two current supplemental submissions is to provide support expanding the ceftaroline fosamil prescribing information for the adult indications of ABSSSI and CABP to include pediatric patients 2 months to <18 years of age. Supportive information for expanding the adult indications to the pediatric population are provided by five pediatric clinical studies and population pharmacokinetic/target attainment report listed below:

1. P903-15: Phase 1, pharmacokinetics of a single dose of ceftaroline fosamil in subject 12 to 17 years of age receiving antibiotic therapy
2. P903-21: Phase 4, pharmacokinetics of a single dose of ceftaroline fosamil in children ages birth to younger than 12 years with suspected or confirmed infection
3. P903-23: Phase 2/3, A multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of ceftaroline versus comparator in pediatric subjects with acute bacterial skin and skin structure infection
4. P903-24: Phase 4, A multicenter, randomized, observer- blinded, active-controlled study evaluating the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline versus ceftriaxone plus vancomycin in pediatric subjects with complicated community-acquired bacterial pneumonia

5. P903-31: Phase 2/3, A multicenter, randomized, observer blinded, active-controlled study evaluating the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline versus ceftriaxone in pediatric subjects with community-acquired bacterial pneumonia requiring hospitalization
6. CPT-MS-08: Population pharmacokinetic modeling update and target attainment simulations for ceftaroline for children ages birth to younger than 18 years

ABSSSI and CABP in adults and children older than 2 months are largely similar with regards to clinical presentation and etiology (i.e., causative pathogens). In addition, there are no expected differences in the mechanism of action based on age because ceftaroline exerts its effects by acting on the causative pathogen. Therefore, once the pharmacokinetics (PK) of ceftaroline are established in the pediatric population, the same pharmacodynamic (PD) principles that were applied for treating adults can be applied to children. In addition, the probability of target attainment using the PK/PD indices and their magnitudes (PK/PD targets) derived from the animal models can be used to confirm the selected dosing regimen for pediatric patients, as conducted in adult patients

A population PK model describing ceftaroline fosamil and ceftaroline, which was developed using the adult Phase 1, 2, and 3 data (Study Report CPT-MS 14), was updated with data from the five pediatric studies aforementioned. This updated population PK model was used to conduct simulations to predict ceftaroline exposures and PK/PD target attainment to determine dose regimens by age and renal function for pediatric patients 2 months to <18 years of age. For pediatric patients ≤2 years old, the renal maturation function (fractional change in clearance due to maturation) was adjusted to allow for simulation of mild, moderate, and severe renal impairment (i.e., it was assumed that renal impairment impacts patients <2 years in the same way that it impacts older patients). Although simulations were conducted to assess doses in pediatric patients with moderate and severe renal impairment, PK data are only available from 1 pediatric patient with CrCl < 50 mL/min/1.73 m^2. Due to the insufficient experience in pediatric patients with moderate or severe renal impairment, the Sponsor did not propose dosing of ceftaroline fosamil for this sub-population.

The proposed dose of ceftaroline fosamil for patients <18 years with normal renal function or mild renal impairment (i.e, CrCl >50 mL/min/1.73 m^2) for the indications of ABSSSI and CABP is listed below. The proposed duration of infusion is 5 minutes to 1 hour.

- Children 2 months to < 24 months: 8 mg/kg q8h
- Children 24 months to < 18 years and ≤ 33 kg: 12 mg/kg q8h
- Children 24 months to < 18 years and > 33 kg: 400 mg q8h

The proposed doses above were either similar or lower than the doses evaluated in the five pediatric clinical studies supporting the two submissions. However, no clinical studies have been conducted to assess the safety, tolerability, and pharmacokinetics of a 5-minute infusion in pediatric patients.

The population PK of ceftaroline fosamil and ceftaroline was described by a combined two compartment model for ceftaroline fosamil and a two-compartment model for ceftaroline. Based

on simulation results, with the proposed doses for pediatric patients, the overall steady-state exposure ($AUC_{24,ss}$) in pediatric patients were observed to be 10 to 80% higher compared to those of adult patients for the same duration of infusion (5-minute or 1-hour). The steady-state maximum concentration ($C_{max,ss}$) in pediatric patients were either similar or up to 45% higher compared to those of adult patients. Please refer to the Key Review Questions for detail.

Target attainment simulation results indicated that the dose regimens proposed by the Sponsor following 5-minute and 1-hour IV infusion, respectively, were predicted to result in the percentage of the duration of unbound drug concentration above MIC in each dosing interval (%fT > MIC) values for an MIC of 1 mg/L similar to or greater than the median model-derived values for adult subjects dosed with the currently approved dose of 600 mg q12h following 5-minute and 1-hour IV infusion, correspondingly. Based on simulations for the proposed dose regimens following 5-minute and 1-hour infusion, >90% of subjects 2 months to < 18 years of age are predicted to achieve PK/PD targets associated with 1-log kill of *S aureus* (36% fT>MIC) and *S pneumonia* (44% fT>MIC), for organisms with MIC values up to 1 mg/L for *S aureus* and 0.5 mg/L for *S pneumonia*, respectively.

Taken together, the Sponsor proposed that the safety, tolerability, and pharmacokinetics data from the five pediatric clinical studies, updated model-based estimation of systemic exposures, and PK/PD target attainment simulations included in these two supplements support the dosing regimens of ceftaroline fosamil for patients age 2 months to < 18 years with normal renal function or mild renal impairment (i.e., CrCl > 50 mL/min/1.73 m^2) for the indications of ABSSSI and CABP.

2. Clinical Pharmacology Assessment and Recommendations:

Based on the findings presented by the Sponsor, the recommendations from the clinical pharmacology team are listed below.

1. The pediatric doses proposed by the Sponsor for patients age 2 months to < 18 years with normal or mild renal function for the indications of ABSSSI and CABP are acceptable.
2. The duration of infusion of 1 hour is acceptable. From a Clinical Pharmacology perspective, the duration of infusion of 5 minutes is acceptable for pediatric patients 6 months to <18 years (see section 3.2). No data or information to support pharmacokinetics, tolerability, or safety of the 5-minute infusion in pediatric patients 2 months to < 6 months, and 2 years to < 18 years were provided in this submission. We recommend the Sponsor obtain additional data supporting the safety, tolerability, and pharmacokinetics of 5 minute or 1 hour infusion in pediatric patients, especially in patients 2 months to < 6 months.

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3. Key Review Questions:

3.1. Does the Sponsor's proposed pediatric dosing regimen result in comparable pediatric ceftaroline exposure ($AUC_{24,ss}$ and $C_{max,ss}$) in patients with normal renal function or mild renal impairment to those observed in adults? Is the pediatric dose proposed by the Sponsor for patients with normal or mild renal function acceptable from a clinical pharmacology perspective?

The simulation results from the population PK model demonstrated that the exposures ($AUC_{24,ss}$ and $C_{max,ss}$) of the active drug, ceftaroline, in pediatric patients age 2 months to <18 years receiving the proposed weight-based dosing were higher (10 to 80% and approximately 45%, respectively) than those in adults receiving a dose of 600 mg every 12 hours. Please refer to the Table 1 below for details.

Table 1. Simulated Median (90% PI) Ceftaroline AUC24,ss and Cmax,ss by Age following the Sponsor'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, 105)	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)

The target attainment simulations indicated that the median percent of the dosing interval that free ceftaroline concentration exceeds the MIC (%fT>MIC) for MIC of 1 mg/L was higher in pediatric patients age 2 months to <18 years with normal renal function or mild renal impairment compared to adult patients with normal renal function for both infusion times. Please refer to Tables 19 through 27 for additional details. In addition, based on the simulations for the proposed dose regimens following 5 minutes and 1 hour infusion, > 90% of subjects 2 months to < 18 years of age are predicted to achieve PK/PD targets associated with 1-log kill of *S aureus* (36% fT>MIC) and *S pneumonia* (44% fT>MIC), for organisms with MIC values up to 1 mg/L for *S aureus* and 0.5 mg/L for *S pneumonia*, respectively.

A total of five clinical studies evaluating ceftaroline fosamil have been conducted in pediatric subjects. Please refer to Table 2 below for additional details. The proposed doses for pediatric patients in current two submissions were either the same or lower than the doses utilized in these

five clinical studies. We defer the safety evaluation to the clinical reviewer. The duration of infusion in these five clinical studies were no less than one hour. As such, clinical data for a 5-minute infusion has not been evaluated in any pediatric clinical studies.

Therefore, with the higher systemic exposure and target attainment than those in adult patients, from a clinical pharmacology perspective (i.e., in terms of efficacy), the proposed pediatric doses for pediatric patients 2 months to < 18 years with normal or mild renal function are acceptable. Please refer to question 2 for the duration of infusion.

Table 2. Five Clinical Studies Evaluating Ceftaroline Fosamil in Pediatric Patients

Study Number	*Study Title*	*Ceftaroline Dose*	*Ceftaroline N*	*Comparator N*
P903-15	Pharmacokinetics of a Single Dose of Ceftaroline in Subjects 12 to 17 Years of Age Receiving Antibiotic Therapy	Children < 75 kg: 8 mg/kg Children ≥ 75 kg: 600 mg	9	–
P903-21	Pharmacokinetics of a Single Dose of Ceftaroline Fosamil in Children Ages Birth to Younger Than 12 Years With Suspected or Confirmed Infection	Cohort 1: (children ≥ 6 years to < 12 years) 10 mg/kg (up to 600 mg for subjects ≥ 60 kg) Cohort 2: (children ≥ 24 months to < 6 years) 15 mg/kg Cohort 3: (children ≥ 28 days and < 24 months) ≥ 5 months: 12 mg/kg and 28 days to 5 months: 8 mg/kg Cohorts 4 and 5: (preterm/term and < 28 days) 8 mg/kg	53	–
P903-23	A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Ceftaroline Versus Comparator in Pediatric Subjects With Acute Bacterial Skin and Skin Structure Infections	Children > 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg Children < 6 months: ceftaroline fosamil 8 mg/kg	107	52
P903-31	A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone in Pediatric Subjects With Community-acquired Bacterial Pneumonia Requiring Hospitalization	Children > 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg Children < 6 months: ceftaroline fosamil 8 mg/kg	121	39
P903-24	A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Ceftaroline Versus Ceftriaxone Plus Vancomycin in Pediatric Subjects with Complicated Community-acquired Bacterial Pneumonia	Children > 6 months: ceftaroline fosamil 15 mg/kg for subjects weighing ≤ 40 kg or 600 mg for subjects weighing > 40 kg Children < 6 months: ceftaroline fosamil 10 mg/kg	30	10
Total number of subjects who received at least 1 dose of study drug			320	101

Source: Study P903-15 CSR, Study P903-21 CSR, Study P903-23 CSR, Study P903-31 CSR, and Study P903-24 CSR.

3.2 Is the proposed duration of infusion, 5 minutes to 1 hour, acceptable from a clinical pharmacology perspective?

Please refer to Question 1 for the simulation results of systemic exposure of ceftaroline and target attainment for the infusion time of 5 minutes and 1 hour.

Based on the results of PK simulations, 5-minute infusion in pediatric patients would result in approximately 40% higher $C_{max,ss}$ compared to 1-hour infusion in the same age group (Table 3). However, no clinical studies have been conducted to assess the safety, tolerability, and pharmacokinetics of 5-minutes infusion in pediatric patients. Thus, there is no data to support the safety of the approximately 40% higher $C_{max,ss}$ in pediatric patients receiving 5-minute infusion. .

Table 3. Comparison of Median Cmax,ss between the Infusion Time of 5 Minutes and 1 hour with the Sponsor's Proposed Doses

12 mg/kg q8h (2-<18 years) and > 33 kg: 400 mg q8h			
age group	Cmax,ss for 1hr infusion (mg/L)	Cmax,ss for 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 for 1hr infusion (mg/L)	Cmax,ss for 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

The safety of 5-minute infusion is potentially supported only in the age group of 6 months to <2 years. In this age group, the Sponsor evaluated the safety, efficacy and PK of ceftaroline fosamil 12 mg/kg q8h administered as 1-hour infusion in two clinical studies (Study P903-23 and P903-31). However, the Sponsor proposed the dose of 8 mg/kg q8h for this age group. The simulation results showed that the $C_{max,ss}$ derived from the dose of 12 mg/kg administered as 1-hour IV infusion in patients 6 months to < 2 years would be similar to that resulted from the dose of 8 mg/kg administered as 5-minute of IV infusion in this group (Table 4). Thus, because the two clinical studies supported the safety of 12 mg/kg as administered 1 hour infusion, the simulation results can indirectly support the safety of the dose of 8 mg/kg administered as 5-minute infusion. However, no data or information to support pharmacokinetics, tolerability, or safety of the 5-minute infusion of the proposed doses in pediatric patients 2 months to < 6 months, and 2 years to < 18 years were provided in the current two submissions. Thus, we recommend the Sponsor obtain additional data supporting the safety, tolerability, and pharmacokinetics of 5 minute in pediatric patients, especially in patients 2 months to < 6 months.

Table 4. Median (90% PI) Steady State Ceftaroline $C_{max,ss}$ Resulted from the Dose of 12 mg/kg q8h Following 1 Hour Infusion and the Dose of 8 mg/kg q8h Following 5 Minute Infusion in Pediatric Patients 6 months to < 2 years with Normal Renal Function Based on Simulations

Age Group	Cmax,ss (mg/L) 12mg/kg 1 hour infusion	Cmax,ss (mg/L) 8mg/kg 5 minute infusion
18-<24 months	28.3	26.3
12-<18 months	28.7	26.4
6-<12 months	29.3	26.6

3.3 Is the proposal not to include dosing recommendations for pediatric patients with CrCL < 50 mL/min/1.73 m^2acceptable?

The Sponsor only included one pediatric patient with moderate renal impairment (30≤ CrCL <50 mL/min/1.73 m^2) in all five pediatric clinical studies. Therefore, the updated population PK model by incorporating data from both pediatric and adult patients (N=720) only contains limited information about this sub-population and may not be able to reliably predict the systemic exposure for the pediatric patients with moderate or severe renal impairment. Moreover, the impact of renal impairment to the kidney development to the pediatric population, especially for patients less than 2 years of age, is not clear.

Therefore, from a clinical pharmacology perspective, we agree with the Sponsor on not recommending any doses for pediatric patients with CrCL < 50 mL/min/1.73 m^2.

4. Individual Study Reviews

4.1 Study P903-15

Title: Pharmacokinetics of a Single Dose of Ceftaroline Fosamil in Subjects 12 to 17 Years of Age Receiving Antibiotic Therapy

This was a Phase 1, multicenter, open-label, non-comparative, single-dose study of ceftaroline fosamil in adolescent subjects 12 to 17 years of age, inclusive, who were hospitalized and receiving antibiotic therapy for treatment of infections of any type. Subjects received a single dose ceftaroline fosamil of 8 mg/kg by IV infusion over 60 (±5) minutes for subjects weighing less than 75 kg (165.4 lb) or 600 mg for subjects weighing 75 kg (165.4 lb) or more. Subjects were to remain in the hospital through 12 hours after the end of infusion. A total of nine subjects were in the Safety Population and eight subjects were in the PK Population in this study. Subject 0003-05001 was not included in the PK population because he experienced extravasation at the infusion site. This patient did not receive the full dose of ceftaroline fosamil and did not have all blood PK samples collected.

Blood for PK analyses was collected immediately before (i.e, within 15 minutes of) the start of the ceftaroline fosamil infusion, 30 minutes after the start of infusion, within 5 minutes before the end of infusion, and at 75 minutes and 2, 3, 6, and 12 hours after the start of the infusion (all time points to be post-infusion).

Urine for PK analyses was collected before the start of the infusion at –2 to 0 hours (± 5 minutes for collection start time and within 5 minutes before the start of the infusion for collection stop time), and after the start of the infusion at 0 to 2 hours, 2 to 6 hours, and 6 to 12 hours (± 5 minutes for collection start and stop times for all intervals) for the three subjects who enrolled under Protocol Amendment 2. Urine for PK analyses was also collected over 12 to 24 hours after infusion of ceftaroline fosamil for the six subjects who enrolled under Protocol Amendment 1.

Subjects were monitored for adverse events (AEs) from the start of infusion of ceftaroline fosamil on Study Day 1 through the follow-up contact on Day 7. Serious adverse events (SAEs) were monitored through 30 days after infusion of ceftaroline fosamil. Medications received from 4 weeks before the start of infusion through Day 7 were recorded. A complete physical examination, hematology and coagulation studies, comprehensive metabolic panel, urinalysis, and urine microscopy were performed at baseline (within 24 hours before the ceftaroline fosamil infusion) and periodically for up to 24 or 12 hours after infusion of ceftaroline fosamil for subjects who enrolled under Protocol Amendment 1 or 2, respectively. Female subjects of childbearing potential underwent urine pregnancy tests at baseline. Vital sign measurements and an electrocardiogram (ECG) were obtained at baseline (Study Day –1 or 1) and periodically for up to 24 or 12 hours after infusion of ceftaroline fosamil for subjects who enrolled under Protocol Amendment 1 or 2, respectively.

4.1.1 Pharmacokinetics Results:

Mean PK parameters for ceftaroline, ceftaroline M-1, and ceftaroline fosamil after infusion of a single dose of ceftaroline fosamil to eight adolescent subjects are presented in Table 5 below.

Subject 0004-15002 was included in the PK population. However, she was observed to have unusually low plasma concentrations of ceftaroline and unusually high plasma concentration of ceftaroline M-1. The Cmax for ceftaroline in this subject was approximately 18% of the mean Cmax in all other subjects in the PK population and the $AUC_{0-\infty}$ for ceftaroline in this subject was 14% of the mean of other subjects. In addition, the $AUC_{0-\infty}$ for ceftaroline M-1 in Subject 0004-15002 was 3.5-times the mean $AUC_{0-\infty}$ for ceftaroline M-1 in other subjects. The Sponsor provided another PK parameter summary excluding subject 0004-15002. Please refer to Table 6 for detail.

Table 5 Pharmacokinetic Parameters (Mean ± SD) for Ceftaroline, Ceftaroline M-1, and Ceftaroline Fosamil Following a Single Intravenous Dose of Ceftaroline Fosamil—PK Population

PK Parameter	*Ceftaroline (N = 8)[a]*	*Ceftaroline M-1 (N = 8)[a]*	*Ceftaroline Fosamil (N = 8)[a]*
AUC_{0-t}, ng•h/mL	38391.81 ± 16063.63	10355.04 ± 7799.51	2293.90 ± 2476.80
$AUC_{0-\infty}$, ng•h/mL	38876.55 ± 16240.87	11186.77 ± 7830.76	NC
C_{max}, ng/mL	15276.14 ± 5996.84	2130.92 ± 2536.78	3272.51 ± 3378.25
T_{max}, h[b]	0.95 (0.48 - 1.00)	1.15 (0.92 - 3.00)	0.50 (0.48 - 0.92)
$T_{½}$, h	1.94 ± 0.27	3.26 ± 0.55	NC
CL, mL/h	14045.58 ± 13409.84	44194.74 ± 16849.96	NC
V_z, mL	35572.84 ± 45126.16	217519.74 ± 94399.62	NC
V_{ss}, mL	43091.61 ± 50837.89	214384.19 ± 89132.43	NC
Ae_{0-t}, mg	211.71 ± 72.38	18.82 ± 8.48	0
Percent recovered in urine (% dose)	56.97 ± 18.23	5.00 ± 2.79	0
CL_r, mL/h	8762.12 ± 10882.35	2003.12 ± 969.70	0

Abbreviations: Ae_{0-t} = amount of ceftaroline excreted in urine during the entire urine collection period from time 0 to time t; AUC_{0-t} = area under the plasma concentration-time curve up to the time corresponding to the last measurable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; CL = plasma clearance; CL_r = renal clearance; C_{max} = maximum (peak) drug concentration in plasma; NC = not calculable; PK = pharmacokinetic; $T_{½}$ = elimination half-life; T_{max} = time of maximum plasma concentration; V_{ss} = volume of distribution at steady-state; V_z = volume of distribution based on the terminal phase.

a Subject 0003-15001 was not included in the PK Population because he experienced extravasation at the infusion site and did not receive the full dose.

b T_{max} values are displayed as the median (range).

Table 6 Pharmacokinetic Parameters (Mean ± SD) for Ceftaroline, Ceftaroline M-1, and Ceftaroline Fosamil Following a Single Intravenous Dose of Ceftaroline Fosamil Excluding Subject 0004- 15002—PK Population

PK Parameter	*Ceftaroline (N = 7)[a]*	*Ceftaroline M-1 (N = 7)[a]*	*Ceftaroline Fosamil (N = 7)[a]*
AUC_{0-t}, ng•h/mL	43050.77 ± 9922.63	7630.14 ± 1292.53	2591.71 ± 2515.79
$AUC_{0-\infty}$, ng•h/mL	43569.02 ± 10110.04	8466.58 ± 1574.58	NC
C_{max}, ng/mL	17031.49 ± 3632.80	1250.07 ± 515.80	3693.58 ± 3414.65
T_{max}, h[b]	0.95 (0.48 - 1.00)	1.30 (0.92 - 3.00)	0.50 (0.48 - 0.92)
$T_{½}$, h	1.86 ± 0.17	3.41 ± 0.39	NC
CL, mL/h	9357.06 ± 2151.11	49133.58 ± 10177.47	NC
V_z, mL	19741.86 ± 6053.73	244761.51 ± 58907.58	NC
V_{ss}, mL	25269.89 ± 7130.52	240572.48 ± 53550.36	NC
Ae_{0-t}, mg	212.71 ± 78.12	17.55 ± 8.29	0
Percent recovered in urine (% dose)	54.76 ± 18.49	4.35 ± 2.28	0
CL_r, mL/h	4954.76 ± 1693.33	2154.77 ± 939.36	NC

Abbreviations: Ae_{0-t} = amount of ceftaroline excreted in urine during the entire urine collection period from time 0 to time t; AUC_{0-t} = area under the plasma concentration-time curve up to the time corresponding to the last measurable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; CL = plasma clearance; CL_r = renal clearance; C_{max} = maximum (peak) drug concentration in plasma; NC = not calculable; PK = pharmacokinetic; $T_{½}$ = elimination half-life; T_{max} = time of maximum plasma concentration; V_{ss} = volume of distribution at steady-state; V_z = volume of distribution based on the terminal phase.

a Subject 0003-15001 was not included in the PK Population because he experienced extravasation at the infusion site and did not receive the full dose of ceftaroline fosamil and did not have all blood PK samples collected. Subject 0004-15002 was included in the PK Population but was not included in the summary statistics because she had unusually low plasma concentrations of ceftaroline and unusually high plasma concentrations of ceftaroline M-1.

b T_{max} values are displayed as the median (range).

4.1.2 Sponsor's Pharmacokinetic Conclusions:

- The mean values of C_{max} and $AUC_{0-\infty}$ for ceftaroline observed in adolescent subjects in this study were about 10% and 23% less than the values observed in adult subjects following a 600-mg dose of ceftaroline fosamil in Study P903-01.
- The ratio of systemic exposure (AUC) of ceftaroline M-1 to ceftaroline and the percentage of the dose excreted in urine as ceftaroline M-1 in adolescent subjects in this study were similar to values observed in adult subjects administered a 600-mg dose of ceftaroline fosamil.
- The ratio of systemic exposure (AUC) of ceftaroline fosamil to ceftaroline in adolescent subjects in this study was similar to the ratio observed in adult subjects administered a 600-mg dose of ceftaroline fosamil.

- As a result of slightly lower systemic exposure in adolescent subjects receiving 8 mg/kg (up to 600 mg for subjects weighing ≥ 75 kg) of ceftaroline fosamil compared with adult subjects receiving 600 mg of ceftaroline fosamil, a modestly higher dose per kilogram should be considered for adolescent subjects aged 12 to 17 years.

Reviewer's Comments: We are in general agreement with the Sponsor's conclusions regarding the PK comparison between adult subjects and adolescent subjects (12-17 years of age). Please refer to Table 7 for the PK parameters of healthy adults (Study P903-01). The safety data was reviewed by Dr. Sheral Patel and we defer the safety issues of ceftaroline to Dr. Patel.

Table 7 Mean ± SD pharmacokinetic parameters following single and multiple 1-h IV infusions of ceftaroline fosamil in healthy adults (P903-01)

Parameter	600 mg Q12h (n=6)	
	Ceftaroline (active)	**Ceftaroline M-1 (open-ring metabolite)**
Single Dose (Day 1)		
C_{max} (µg/mL)	18.97 ± 0.71	2.72 ± 0.77
T_{max} (h)[a]	1.00 (0.92-1.25)	1.00 (0.67-5.00)
AUC_{inf} (µg*h/mL)	56.79 ± 9.31	15.80 ± 3.21
$t_{1/2}$ (h)	1.60 ± 0.38	3.50 ± 1.36
CL (L/h)	9.58 ± 1.85	35.63 ± 6.60
V_z (L)	21.97 ± 5.43	177.1 ± 60.5
Multiple Dose (Day 14)		
C_{max} (µg/mL)	21.33 ± 4.10	3.58 ± 0.62
T_{max} (h)[a]	0.92 (0.92-1.08)	1.08 (0.92-1.53)
AUC_{tau} (µg*h/mL)	56.25 ± 8.90	18.95 ± 4.62
$t_{1/2}$ (h)	2.66 ± 0.40	6.84 ± 0.59
CL (L/h)	9.60 ± 1.40	30.05 ± 6.40
V_z (L)	35.30 ± 7.40	221.5 ± 73.1
Accumulation Ratio	1.03 ± 0.12	1.46 ± 0.10

[a] T_{max} reported as median (minimum-maximum)
Accumulation ratio, AUC_{tau} ratio of Day 14 to Day 1; **AUC_{inf},** area under concentration-time curve from time 0 to infinity; **AUC_{tau},** area under concentration-time curve over dosing interval; **C_{max},** maximum observed concentration; **CL**, plasma clearance; **$t_{1/2}$,** elimination half-life; **T_{max},** time of maximum observed concentration; **V_z,** apparent volume of distribution of terminal phase

4.2 Study P903-21

Title: Pharmacokinetics of a Single Dose of Ceftaroline fosamil in Children Ages Birth to Younger than 12 Years With Suspected or Confirmed Infection

Study P903-21 is a Phase 4, multicenter, open-label, sequential, single-dose, prospective study of ceftaroline fosamil in subjects younger than 12 years with a suspected or confirmed bacterial infection. A total of 53 subjects enrolled in the study and all of them completed treatment and were evaluated for PK analysis. One out of these 53 subjects was lost to follow up. Fifty-three subjects received ceftaroline and were included in the Safety Population.

These 53 subjects were stratified into five sequential cohorts with chronological ages from birth to younger than 12 years as shown below:

- Cohort 1: children ages ≥ 6 years to < 12 years

- Cohort 2: children ages ≥ 24 months to < 6 years
- Cohort 3: young infants and toddlers ages ≥ 28 days to < 24 months (with equal representation of subjects aged 28 days to < 12 months [Cohort 3B] and 12 months to < 24 months [Cohort 3A])
- Cohort 4: term (gestational age ≥ 38 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days [Cohort 4B] and > 14 days to < 28 days [Cohort 4A])
- Cohort 5: preterm (gestational age 32 to 37 weeks) neonates ages < 28 days (stratified within the group as 0 to 14 days [Cohort 5B] and > 14 days to < 28 days [Cohort 5A])

Subjects in each cohort received a single infusion of IV cefteroline fosamil at the following doses shown below:

- Cohort 1: 10 mg/kg (up to 600 mg for subjects ≥ 60 kg) ceftaroline fosamil as a 1-hour infusion
- Cohort 2: 15 mg/kg ceftaroline fosamil as a 90-minute infusion
- Cohort 3: ≥ 5 months: 12 mg/kg ceftaroline fosamil as a 1-hour infusion; 28 days to 5 months: 8 mg/kg ceftaroline fosamil as a 1-hour infusion
- Cohorts 4 and 5: 8 mg/kg ceftaroline fosamil as a 1-hour infusion

Blood samples were obtained for analysis of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 plasma concentrations at the following times:

- At the end of infusion (±5 minutes)
- 15 to 45 minutes from end of infusion
- 3 to 4 hours from end of infusion
- 5 to 7 hours from end of infusion

A limited PK sampling scheme (4 samples from each subject) was employed and no more than 0.6 mL of plasma were obtained for each PK sample. The exact time of PK sample collection was recorded. After at least 4 evaluable subjects (defined as subjects who received the entire dose of ceftaroline fosamil and from whom at least 3 PK samples were collected) were enrolled in each cohort (up to and including Cohort 3), PK samples from these subjects were analyzed to obtain plasma concentrations and the data were added to population PK models for ceftaroline and ceftaroline fosamil. The models were adjusted as necessary to accommodate the new data and then used to predict exposure measures (maximum concentration [Cmax], area under the curve for plasma concentration versus time [AUC], and percent of time above minimum inhibitory concentration [%T > MIC]) in the next youngest cohort in order to select a dose. Results of these analyses were reviewed, along with available safety data, by the Internal Data Review Committee (IDRC) before dosing of the next youngest cohort began.

Fifty-three subjects received ceftaroline fosamil and were included in the Safety Population. There were no deaths and no subjects discontinued from the study due to an adverse event (AE).

4.2.1 Pharmacokinetics Results:

No individual PK parameters were calculated for this study. Mean plasma concentrations of ceftaroline in each collection interval are summarized in Table 8, by cohort and by age subgroup within Cohorts 3, 4, and 5. The data for ceftaroline fosamil and ceftaroline M-1 are not presented

here. Plasma concentration data for ceftaroline and ceftaroline fosamil were pooled with data from other studies in adults and adolescent subjects in a population PK analysis that is reported separately.

Table 8 Mean Ceftaroline Plasma Concentration by Cohort

Mean Ceftaroline Plasma Concentrations by Cohort

Collection Times	*Mean (±SD) Ceftaroline Plasma Concentration (ng/mL)*				
	Cohort 1 (n = 10)	*Cohort 2 (n = 8)*	*Cohort 3 (n = 12)*	*Cohort 4 (n = 12)*	*Cohort 5 (n = 11)*
At end of infusion (± 5 minutes)	18325.08 ± 3563.06	23052.72 ± 5485.06	16938.90 ± 3693.24	10530.69 ± 2529.54	11091.64 ± 1505.90[a]
15 to 45 minutes from end of infusion	12114.21 ± 3157.54	14860.30 ± 3448.84	12549.92 ± 2861.96	9782.58 ± 2013.87[b]	10348.61 ± 1064.83[a]
3 to 4 hours from end of infusion	2769.49 ± 890.70	3626.51 ± 1663.57	3286.77 ± 1215.47	4600.61 ± 819.13	5061.97 ± 1668.45
5 to 7 hours from end of infusion	1138.30 ± 489.43	1600.83 ± 641.75	1573.37 ± 688.59	2687.71 ± 623.84	3115.87 ± 1350.72

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

a n = 9.

b n = 11.

Mean Ceftaroline Plasma Concentrations by Age Subgroup Within Cohorts 3, 4, and 5

Collection Times	*Mean (±SD) Ceftaroline Plasma Concentration (ng/mL)*					
	Cohort 3A (n = 9)	*Cohort 3B (n = 3)*	*Cohort 4A (n = 6)*	*Cohort 4B (n = 6)*	*Cohort 5A (n = 5)*	*Cohort 5B (n = 6)*
At end of infusion (± 5 minutes)	17574.86 ± 4089.45	15031.02 ± 919.52	10808.87 ± 1995.66	10252.51 ± 3147.78	11168.62 ± 1599.43[a]	11030.05 ± 1614.37[b]
15 to 45 minutes from end of infusion	13183.51 ± 3045.91	10649.14 ± 844.47	9746.93 ± 1379.36	9825.35 ± 2785.08[b]	9848.78 ± 1535.71[a]	10748.48 ± 221.83[b]
3 to 4 hours from end of infusion	3440.01 ± 1360.72	2827.07 ± 544.61	4280.58 ± 870.61	4920.64 ± 687.30	3807.40 ± 1293.25	6107.45 ± 1159.26
5 to 7 hours from end of infusion.	1626.06 ± 786.01	1415.30 ± 294.35	2314.60 ± 381.99	3060.82 ± 613.34	2340.73 ± 1008.17	3761.81 ± 1316.91

Notes: Cohort substrata: 3A = 5 months to < 24 months, administered 12 mg/kg; 3B = 28 days to < 5 months, administered 8 mg/kg; 4A = term neonates > 14 days to < 28 days, administered 8 mg/kg; 4B = term neonates 0 to 14 days, administered 8 mg/kg; 5A = preterm neonates > 14 days to < 28 days, administered 8 mg/kg; 5B = preterm neonates 0 to 14 days, administered 8 mg/kg.

a n = 4.

b n = 5.

Reviewer's Comment: It was observed that the Cmax achieved by receiving 12 mg/kg one hour of IV infusion for the age group of ≥ 5 months to < 24 months was lower than expected (i.e. simulated median Cmax,ss after 1 hour of 12 mg/kg infusion was about 29 mg/L; the observed mean Cmax,single dose was about 18 mg/L;). Based on the output of final model (Run 118), the individual predicted plasma concentrations were similar to the observed ones for Study 21. Part of the reason for simulated Cmax,ss higher than the observed Cmax, single dose may be due to

the accumulation after multiple doses. However, since the half-life of ceftaroline is short, about 2 hours, accumulation may not be the only reason. The reviewer also noted that some of the sampling time in Study 21 for Cmax was delayed to 10 minutes post infusion instead of ± 5 minutes.

Ceftaroline was measureable in all PK samples collected from all subjects. All subjects had ceftaroline plasma concentrations > 1 mg/L in plasma samples collected 3 to 4 hours after the end of the ceftaroline fosamil infusion (4 to 5 hours from the beginning of infusion), and the majority of subjects (45 out of 53) had ceftaroline concentrations > 1 mg/L in plasma samples collected 5 to 7 hours after the end of infusion.

The mean ceftaroline concentrations in the plasma samples taken at the end of the ceftaroline fosamil infusion, which should represent the approximate Cmax, were lower in Cohorts 4 and 5 than in Cohorts 1, 2, and 3. This was expected based on the lower dose in Cohorts 4 and 5; however, the lower dose may not fully explain the lower Cmax. In contrast, the mean ceftaroline concentrations in PK samples taken in the last collection interval (5 to 7 hours after the end of the ceftaroline fosamil infusion) were higher for Cohorts 4 and 5 compared to Cohorts 1, 2, and 3. Within Cohorts 4 and 5, ceftaroline plasma concentrations in the last 2 PK sample collection intervals tended to be higher in subjects with an age range of birth to 14 days than in subjects > 14 to < 28 days, again suggesting that maturation of renal function may impact ceftaroline clearance in the youngest subjects.

Ceftaroline fosamil plasma concentrations were variable, and were typically only measureable in plasma samples taken at the end of the ceftaroline fosamil infusion or 15 to 45 minutes after the end of infusion. This is expected based on the rapid conversion of ceftaroline fosamil to ceftaroline in plasma.

Ceftaroline M-1 was measureable in all PK samples collected from all subjects. The highest mean ceftaroline M-1 plasma concentration occurred in plasma samples collected 3 to 4 hours after the end of the ceftaroline infusion. This is consistent with data in healthy adult subjects in which time to maximum drug concentration (Tmax) for ceftaroline M-1 typically occurred around 3 hours. At the end of infusion, mean ceftaroline M-1 plasma concentrations in each cohort were approximately 3% to 4% of mean ceftaroline plasma concentrations at the same time. For plasma samples collected 5 to 7 hours after the end of infusion, mean ceftaroline M-1 levels were 53.3%, 50.3%, 51.1%, 26.0%, and 25.7% of mean ceftaroline levels at the same time for Cohorts 1, 2, 3, 4, and 5, respectively. The higher percentages in this collection interval are reflective of the longer half-life of ceftaroline M-1 compared to ceftaroline (approximately 4 hours and 2.5 hours, respectively, in healthy adults).

4.2.2 Sponsor's Pharmacokinetic Conclusions:

- The doses used in this study achieved ceftaroline exposures in pediatric subjects that exceeded the minimum concentration required to inhibit the growth of 90% of organisms (MIC90) for ceftaroline against *Staphylococcus aureus* for more than 50% of an 8-hour dosing interval.

- It was observed that ceftaroline was cleared more slowly by the youngest subjects (cohort 4 and cohort 5). Because ceftaroline is predominantly cleared by the kidneys, this observation is consistent with immature renal function in this younger age range.

4.3 Study P903-23

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

This was a phase 2/3 multicenter, randomized, observer-blinded, active-controlled, parallel-group study to evaluate the efficacy, safety, and PK of intravenous (IV) ceftaroline versus IV comparator (vancomycin or cefazolin with or without aztreonam) in pediatric subjects from the ages of 2 months to < 18 years with ABSSSI. Aztreonam was available for administration, if required, during IV treatment with comparator, if an infection involving a Gram-negative pathogen was identified or suspected. Subjects were stratified by age cohort and region and were randomly assigned to treatment in a 2:1 ratio, ceftaroline to comparator. The following age cohorts were defined:

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

IV ceftaroline fosamil was infused over 60 (± 10) minutes every 8 hours (q8h) (± 1 hour) as follows:

- Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg
- Children < 6 months: ceftaroline fosamil 8 mg/kg

A minimum of 7 IV doses was required for subjects randomized to ceftaroline group. Subjects may have been switched from IV to open-label oral study drug (cephalexin at 25 mg/kg q6h [preferred switch], clindamycin 10 mg/kg q8h, or linezolid [600 mg every 12 hours (q12h) [Cohort 1] or 10 mg/kg q8h [Cohorts 2, 3, and 4]) on or after Study Day 4.

Total duration of study drug therapy (IV and oral, or IV alone) was 5 to 14 days; a minimum of 3 days (7 infusions for subjects randomized to ceftaroline fosamil) of IV study drug therapy was required. The total duration of subject participation was expected to be 26 to 50 days.

Number of Subjects:
Please see Table 9 for detail.

Table 9 Subject Populations

Population	*Ceftaroline N*	*Comparator N*	*Total N*
ITT Population	110	53	163
Safety Population	106	53	159
MITT Population	107	52	159
mMITT Population	52	22	74
CE Population	96	45	141
ME Population	46	17	63
PK Population	99	NA	99

Abbreviations: CE = Clinically Evaluable; ITT = Intent-to-Treat; MITT = Modified Intent-to-Treat; mMITT = Microbiological MITT; ME = Microbiologically Evaluable; PK = Pharmacokinetic.

Source: Table 14.1.1.1 and Appendix 16.5 (PK Population).

4.3.1 Pharmacokinetic Measurements and Analyses

A sparse PK sampling schedule was applied to this study and only at selected study centers. Samples were to be collected between the end of the fourth infusion of ceftaroline fosamil and before the oral switch or Study Day 5 (whichever was earlier). The PK blood samples were not to be drawn if the subject had received a blood or blood component transfusion within the past 24 hours.

- 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)

The PK samples were to be collected from subjects in the ceftaroline group and analyzed (using a validated assay) by the unblinded central bioanalytical laboratory. In summary, plasma concentrations were determined using a liquid chromatography coupled with tandem mass spectrometry method that was validated to demonstrate the accuracy, linearity, reproducibility, and precision of the analytical procedure. The method has a lower limit of quantification for all analytes of 50 ng/mL.

A total of 198 plasma samples from 99 subjects in the ceftaroline treatment group were analyzed to determine concentrations of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 (inactive, open ring metabolite). Cerebral spinal fluid samples were not taken from any subject; therefore, none were available for analyses. Ceftaroline and ceftaroline fosamil 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 is reported separately. No PK parameters were calculated in this study.

4.4 Study P903-24

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

This was a Phase 4, multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, PK, and efficacy of intravenous (IV) ceftaroline fosamil versus IV ceftriaxone plus IV vancomycin (referred to as comparators) in pediatric subjects aged 2 months to < 18 years with complicated CABP, which was designed to enrich for subjects at risk for infection due to MRSA. Block randomization, stratified by age cohort, was used to assign subjects (3:1) to ceftaroline fosamil or comparators. The following age cohorts were defined:

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

Subjects were to receive at least 5 days, but no more than 21 days of study drug therapy (IV [ceftaroline fosamil or comparators] or IV plus oral combined; a minimum of 3 days [72 hours] of IV study drug was required). Vancomycin could be discontinued on or after Study Day 4 if MRSA, penicillin-resistant Streptococcus pneumoniae (PRSP), or penicillin-intermediate S. pneumoniae (PISP) was not confirmed or suspected. A switch to open-label oral study drugs (amoxicillin clavulanate, clindamycin, or linezolid) was allowed on or after Study Day 4 if the subject met the protocol-specified criteria.

Intravenous ceftaroline fosamil infused over 120 (± 10) min every 8 hours (q8h) (± 1 hour) as follows:

- Children ≥ 6 months: ceftaroline fosamil 15 mg/kg for subjects weighing ≤ 40 kg or 600 mg for subjects weighing > 40 kg
- Children < 6 months: ceftaroline fosamil 10 mg/kg

Total duration of study drug therapy was 5 to 21 days; a minimum of 3 days of initial hospitalization and 3 days (72 hours) of IV study drug therapy (ceftaroline fosamil or comparators) were required. The total duration of subject participation was expected to be 26 to 57 days; the Late Follow-up (LFU) assessments were to occur 21 to 35 days after last dose of any study drug (IV or oral).

Number of Subjects:
Intent-to-Treat (ITT) Population: 30 subjects randomized to ceftaroline fosamil, 10 subjects randomized to comparators
Analyzed for efficacy:

- Modified Intent-to-Treat (MITT) Population: 29 ceftaroline fosamil; 9 comparators
- Clinically Evaluable (CE) Population: 26 ceftaroline fosamil; 9 comparators
- Microbiological Modified Intent-to-Treat (mMITT) Population: 15 ceftaroline fosamil; 3 comparators

- Microbiologically Evaluable (ME): 13 ceftaroline fosamil; 3 comparators

Analyzed for Safety:

- Safety Population: 30 ceftaroline fosamil; 10 comparators

PK population:

- PK population: N=29; All randomized subjects who received a known amount of ceftaroline fosamil and who had at least 1 PK sample collected (excluding those who received blood or blood component transfusions within 24 hours before any PK sample was drawn).

4.4.1 Pharmacokinetic Measurements and Analyses

A sparse PK sampling schedule was applied to this study. Samples were to be collected between the end of the fourth infusion of ceftaroline fosamil and before the oral switch or Study Day 5 (whichever was earlier). The PK blood samples were not to be drawn if the subject had received a blood or blood component transfusion within the past 24 hours.

- 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)

The PK samples were to be collected from subjects in the ceftaroline group and analyzed (using a validated assay) by the unblinded central bioanalytical laboratory. In summary, plasma concentrations were determined using a liquid chromatography coupled with tandem mass spectrometry method that was validated to demonstrate the accuracy, linearity, reproducibility, and precision of the analytical procedure. The method has a lower limit of quantification for all analytes of 50 ng/mL.

Plasma concentrations of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 were listed for each subject in the PK population. Ceftaroline and ceftaroline fosamil 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. This analysis is presented in a separate report. No PK parameters were calculated or reported for this study.

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4.5 Study P903-31

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

This was a Phase 2/3 multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, PK, and efficacy of ceftaroline versus ceftriaxone in pediatric subjects aged 2 months to < 18 years with CABP requiring hospitalization. Subjects were

stratified by age cohort and region and were randomly assigned to treatment in a 3:1 ratio, ceftaroline fosamil to ceftriaxone. The following age cohorts were defined:

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

A minimum of 7 intravenous (IV) doses was required for subjects randomized to ceftaroline fosamil. A switch to open label oral study drug (amoxicillin clavulanate) was allowed on or after Study Day 4 if a subject met the protocol-specified criteria.

IV ceftaroline fosamil infused over 60 (± 10) minutes every 8 hours (q8h [± 1 hour]) as follows:

- Children ≥ 6 months: ceftaroline fosamil 12 mg/kg for subjects weighing ≤ 33 kg or 400 mg for subjects weighing > 33 kg
- Children < 6 months: ceftaroline fosamil 8 mg/kg

Total duration of study drug therapy was 5 to 14 days, inclusive; a minimum of 3 days (7 infusions for subjects randomized to ceftaroline fosamil) of IV study drug therapy was required. The total duration of subject participation was expected to be 26 to 50 days, inclusive.

Number of Subjects:
Intent-to-Treat (ITT) Population: 122 subjects ceftaroline fosamil, 39 subjects ceftriaxone.
Analyzed for efficacy:

- Modified Intent-to-Treat (MITT) Population: 107 ceftaroline fosamil; 36 ceftriaxone
- Microbiological Modified Intent-to-Treat (mMITT) Population: 24 ceftaroline fosamil; 9 ceftriaxone
- Clinically evaluable (CE) Population: 98 ceftaroline fosamil; 36 ceftriaxone
- Microbiologically evaluable (ME) Population: 23 ceftaroline fosamil; 9 ceftriaxone

Analyzed for safety:

- Safety Population: 121 ceftaroline fosamil; 39 ceftriaxone

PK population:

- PK population: N=116; All randomized subjects who received a known amount of ceftaroline fosamil and who had had at least 1 PK sample collected (excluding those who received blood or blood component transfusions within 24 hours before any PK sample was drawn)

4.5.1 Pharmacokinetic Measurements and Analyses

A sparse PK sampling schedule was applied to this study. Samples were to be collected between the end of the fourth infusion of ceftaroline fosamil and before the oral switch or Study Day 5 (whichever was earlier). The PK blood samples were not to be drawn if the subject had received a blood or blood component transfusion within the past 24 hours.

- 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)

The PK samples were to be collected from subjects in the ceftaroline group and analyzed (using a validated assay) by the unblinded central bioanalytical laboratory.

Plasma concentrations of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 were listed for each subject by age cohort in the PK Population. Ceftaroline and ceftaroline fosamil 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. This analysis is reported separately.

4.6 Population PK Analysis Report
Title: CPT-MS-08: Population Pharmacokinetic Modeling Update and Target Attainment Simulations for Ceftaroline for Children Ages Birth to Younger Than 18 Years

The objective of the population PK analysis is to describe the population pharmacokinetics of ceftaroline and ceftaroline fosamil in pediatric patients.

4.6.1 Source Data
This population PK analysis evaluated data obtained from the studies listed below and all other studies in healthy volunteers and patient adults and adolescents used in previous population PK modeling (Study CPT-MS-14). The five individual studies listed below have been summarized previously in this review.

1. P903-15: Phase 1, pharmacokinetics of a single dose of ceftaroline fosamil in subject 12 to 17 years of age receiving antibiotic therapy
2. P903-21: Phase 4, pharmacokinetics of a single dose of ceftaroline fosamil in children ages birth to younger than 12 years with suspected or confirmed infection
3. P903-23: Phase 2/3, A multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of ceftaroline versus comparator in pediatric subjects with acute bacterial skin and skin structure infection
4. P903-24: Phase 4, A multicenter, randomized, observer- blinded, active-controlled study evaluating the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline versus ceftriaxone plus vancomycin in pediatric subjects with complicated community-acquired bacterial pneumonia
5. P903-31: Phase 2/3, A multicenter, randomized, observer blinded, active-controlled study evaluating the safety, tolerability, pharmacokinetics, and efficacy of ceftaroline versus ceftriaxone in pediatric subjects with community-acquired bacterial pneumonia requiring hospitalization

4.6.2 Bioanalytical Methods

The assay method used was validated to demonstrate the selectivity, accuracy, linearity, reproducibility, and precision of the analytical procedure. Complete details of the assay methodology and performance for each of these studies are provided in the original NDA submission.

In Studies P903-15 and P903-21, the plasma samples collected were assayed by (b) (4) and for Studies P903-23, P903-24, and P903-31, the samples were assayed by (b) (4). A Biopharmaceutical Inspection for these two sites was requested by the Clinical Pharmacology reviewer on February 19, 2016.

4.6.3 Data Assembly

All concentrations reported as below the limit of quantification (BLQ) were set to an EVID and MDV value of 0 and identified in the data set with a flag (BLQ=1). Any measurable concentrations occurring prior to the first dose were commented out of the data set. Individual, clinical, and demographic covariate factors were also included in the population data set. If greater than 10% of any covariate value is missing, that covariate was not included in the analysis. Otherwise, missing covariates were imputed using a single imputation method, based on the remaining available data (typically with the median of remaining values). Ceftaroline or ceftaroline fosamil concentration observations with missing observation or dosing times were not included in the analysis.

PK data included ceftaroline and ceftaroline fosamil concentration measurements in plasma and associated observation times.

Covariates to be included in the dataset included age, weight, sex, patient type (healthy subjects versus patients), body surface area (BSA), creatinine clearance (CRCL), and CRCL normalized by BSA (nCRCL). Derived covariates, such as BSA, CRCL and nCRCL were calculated from the observed covariates according to equations 1, 2, 3, and 4 listed below. Equation 2 and 3 were used to calculate the CRCL for adults. Equation 4, the Schwartz method (bedside formula) was used to calculate creatinine clearance for pediatric patients in studies P903-21, -23, -24, and -31.

Equation 1

(b) (4)

4.6.4 Analysis Population and Data Characteristics

The ceftaroline population PK dataset was comprised of 525 patients and 195 healthy subjects contributing a total of 10,884 concentrations (5410 ceftaroline fosamil and 5474 ceftaroline). After accounting for concentrations that were BLQ, there were 6633 concentrations (1799 ceftaroline fosamil and 4834 ceftaroline) available for analysis. Of the 525 patients in the analysis data set, the 305 pediatric patients from Studies P903-15, -21, -23, -24, and -31 contributed a total of 974 measurable concentrations (234 ceftaroline fosamil and 740 ceftaroline). The dataset included patients with complicated skin and skin structure infections or community acquired pneumonia; pediatric patients with complicated skin and skin structure infections, community acquired pneumonia, or an infection of any type; and healthy subjects.

The studies contributing pediatric data consisted of 173 males and 132 females with ages ranging from 1 day to 17 years and bodyweights ranging from 1.5 to 100 kg. In the pediatric population with a reported nCRCL, there were 241(85.5%), 40(14.2%), and 1(0.3%) patients with nCRCL ≥80, 50-<80, and 30-<50 ml/min/1.73m^2, respectively. The 23 neonates (to-term and preterm) did not have a reported nCRCL.

For adults, the breakdown was 268 males and 147 females with ages ranging from 18 to 88 years and bodyweights ranging from 40 to 134 kg. Distributions of all continuous covariates were similar across both sexes and between healthy subjects and patients with the following exceptions: i) males exhibited a slightly higher median weight and BSA than females; and ii) patients exhibited a lower median age, weight, body mass index (BMI), and BSA than healthy subjects due to the inclusion of the pediatric patients. Please refer to Tables 10, 11, 12, and 13 for the summary of the demographic statistics.

Table 10. Summary of Continuous Covariates by Patient Status for Adults

PAT	covariate	N	minimum	maximum	median	mean
0	Weight (kg)	195	45.00	115.00	75.00	77.20
0	BMI (kg/m^2)	195	18.90	32.40	24.80	24.90
0	BSA (m^2)	195	1.40	2.44	1.91	1.93
0	Age (yr)	195	18.00	81.00	31.00	37.50
0	nCRCL $(mL/min/1.73m^2)$	195	8.20	168.00	95.30	88.90
1	Weight (kg)	220	40.00	134.00	74.00	75.60
1	BMI (kg/m^2)	220	17.50	38.20	24.40	24.90
1	BSA (m^2)	220	1.28	2.58	1.89	1.89
1	Age (yr)	220	18.00	88.00	53.00	51.40
1	nCRCL $(mL/min/1.73m^2)$	220	26.00	269.00	90.10	93.50

PAT = 1 for patients and 0 for healthy subjects

Adapted from the Sponsor's report of Study CPT-MS-08, Table 11

Table 11. Summary of Renal Function Groups by Patient Status in Adults

PatientStatus	stat	1	2	3	4	5
0	Number	131.0	39.0	11.0	8.0	6.0
0	Percentage	67.2	20.0	5.6	4.1	3.1
1	Number	129.0	68.0	22.0	1.0	
1	Percentage	58.6	30.9	10.0	0.5	

PatientStatus = 1 for patients and 0 for healthy subjects, RF = 1 for normal, 2 for mild impairment, 3 for moderate impairment, 4 for severe impairment, and 5 for ESRD.

Adapted from the Sponsor's report of Study CPT-MS-08, Table 13

Table 12. Summary of Age Groups for Pediatric Patients

AgeGroup	stat	0	1
preterm neonates	Number	9.0	2.0
preterm neonates	Percentage	81.8	18.2
to-term neonates	Number	6.0	6.0
to-term neonates	Percentage	50.0	50.0
28d-<2yr	Number	40.0	24.0
28d-<2yr	Percentage	62.5	37.5
2-<6yr	Number	57.0	45.0
2-<6yr	Percentage	55.9	44.1
6-<12yr	Number	41.0	33.0
6-<12yr	Percentage	55.4	44.6
12-<18yr	Number	20.0	22.0
12-<18yr	Percentage	47.6	52.4

Sex = 0 for male and 1 for female.

Adapted from the Sponsor's report of Study CPT-MS-08, Table 19

Table 13. Summary of Renal Function Groups for Pediatric Patients

AgeGroup	stat	1	2	3	4
28d-<2yr	Number	48.0	15.0	1.0	
28d-<2yr	Percentage	75.0	23.4	1.6	
2-<6yr	Number	88.0	14.0		
2-<6yr	Percentage	86.3	13.7		
6-<12yr	Number	65.0	9.0		
6-<12yr	Percentage	87.8	12.2		
12-<18yr	Number	40.0	2.0		
12-<18yr	Percentage	95.2	4.8		

RF = 1 for normal (≥80 $mL/min/1.73m^2$), 2 for mild impairment (50-<80 $mL/min/1.73m^2$), 3 for moderate impairment (30-<50 $mL/min/1.73m^2$), 4 for severe impairment (15-<30 $mL/min/1.73m^2$). To-term and preterm neonates are not present in this table because a nCRCL was not reported for these age groups.

Adapted from the Sponsor's report of Study CPT-MS-08, Table 20

The pop-PK model developed for adult subjects, shown in equation 5, was modified to include an effect renal maturation on ceftaroline central compartment clearance (CLc) to account for renal maturation in pediatric patients less than 2 years old. The model was also modified to allow for the maturational change in the volume of distribution of ceftaroline central compartment (Vcc). Please refer to equation 6 for the final model.

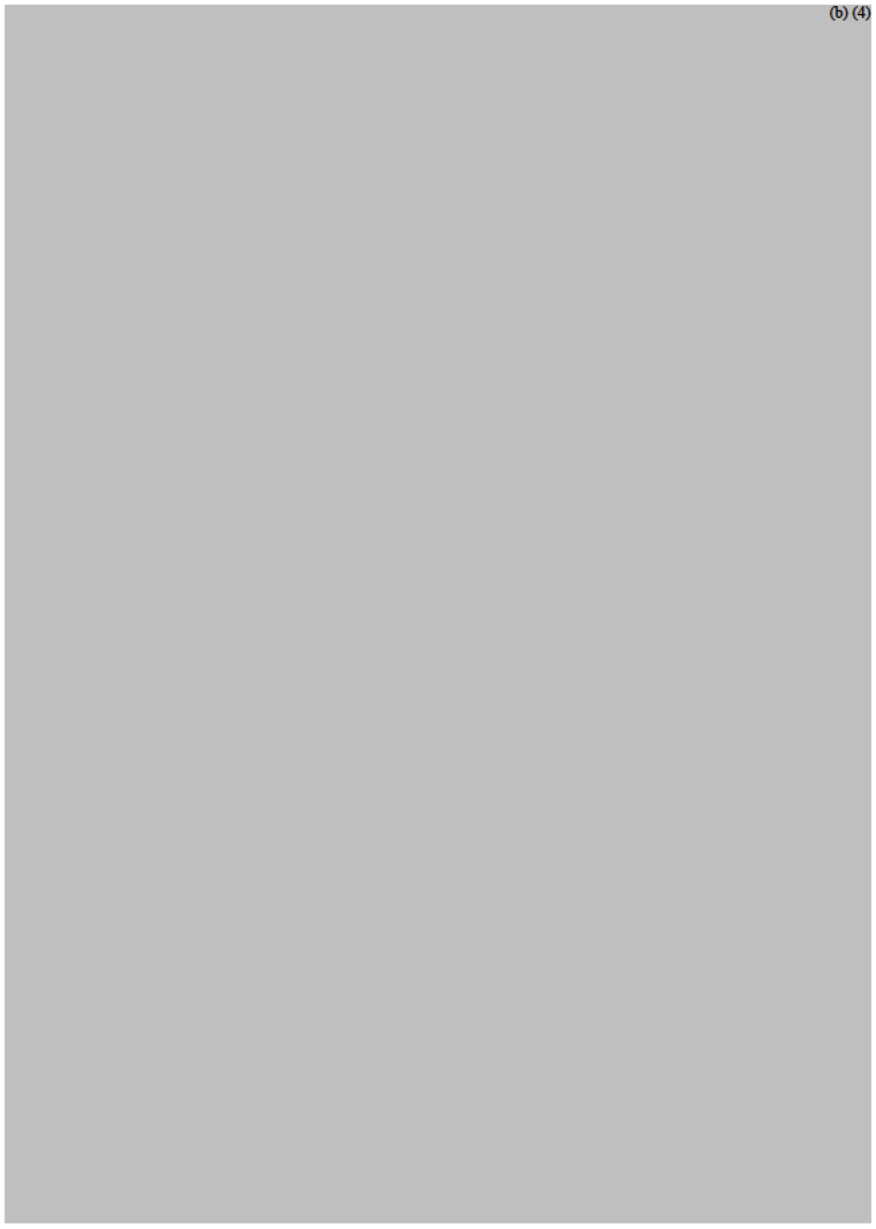
Reviewer's Comment: The Sponsor updated a previously developed adult only population PK model with the maturation factors for both ceftaroline central compartment clearance (CLc) and the volume of distribution of central compartment (Vcc) to describe exposures in pediatric patients. The structure of maturation factor for CLc followed the publication of Holford's group in 2009[1]. The structure of maturation factor for Vcc was modified following the publication of Holford's group in 2002[2]. The addition of the maturation factors seems reasonable.

[1] Rhodin MM et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol (2009) 24:67-76

[2] Anderson BJ et al. Acetaminophen developmental pharmacokinetics in premature neonates and infants. Anesthesiology (2002) 96: 1336-45

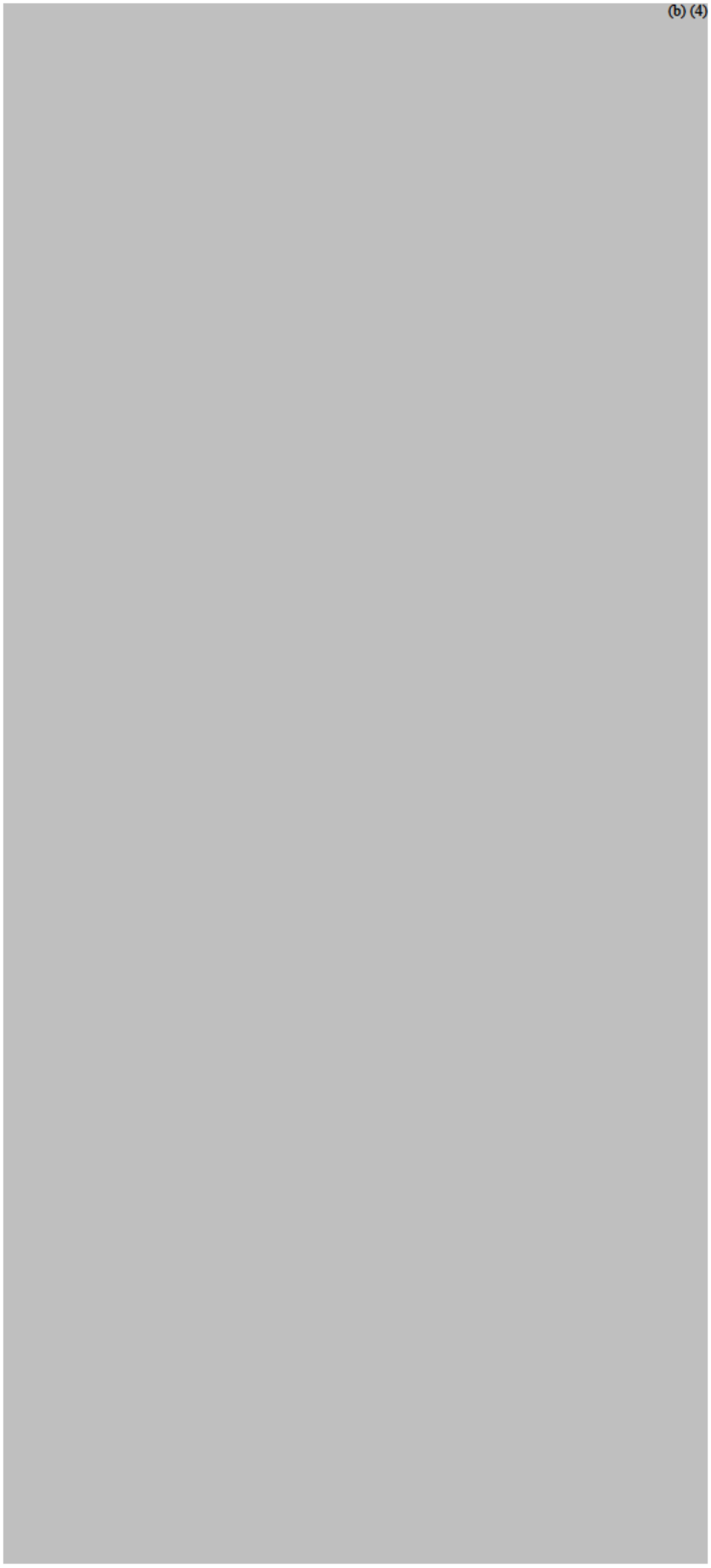
Equation 5

Pharmacokinetic Final Model (Run 108 - original scale)



Equation 6
Final Pharmacokinetic Model after adding in pediatric patients data

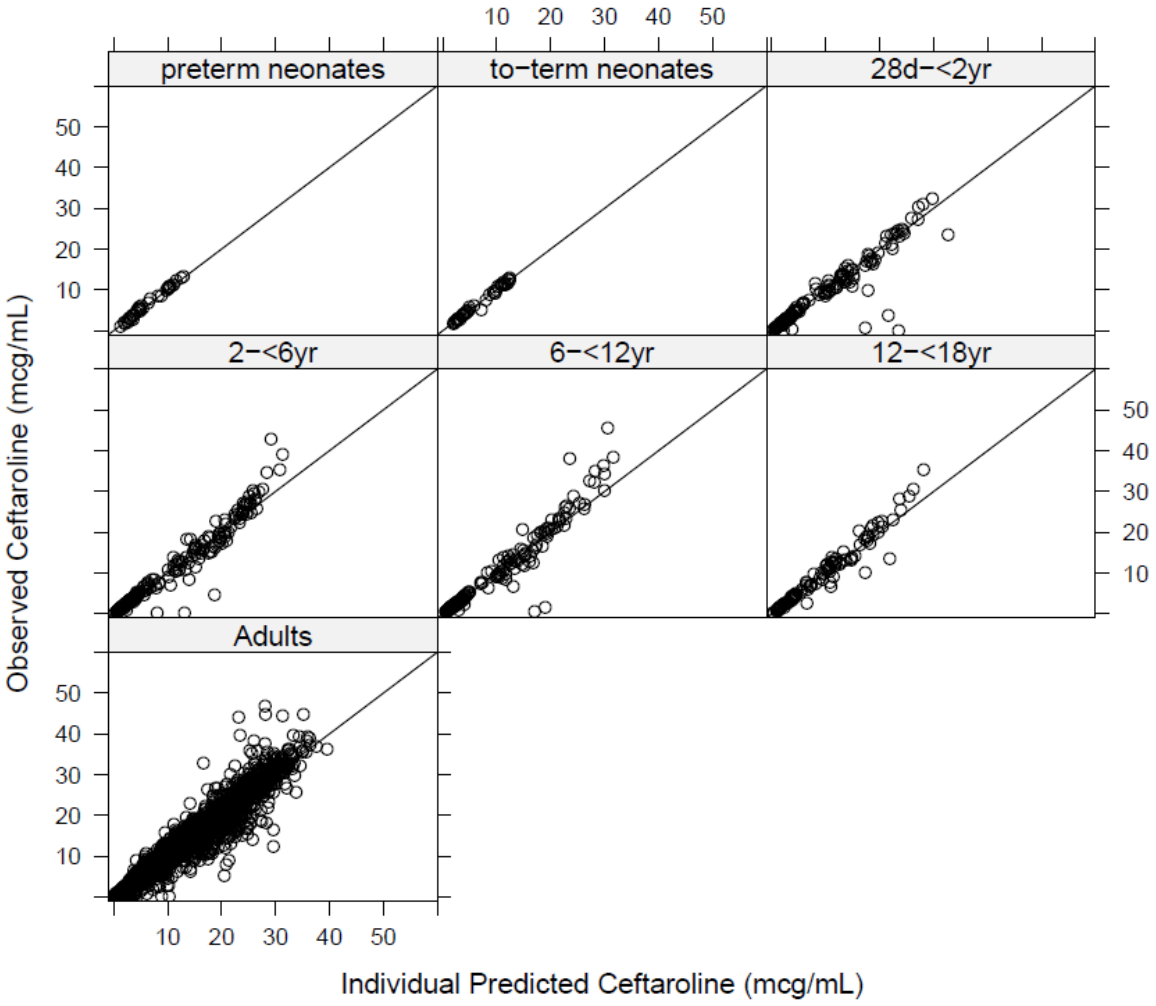
(b) (4)



The final model resulted in imporved goodness-of-fit criteria across all pediatric age groups (see Figure 1).

Figure 1 Observed vs. Individual Predicted Ceftaroline by Age Group (Run 118, final model)

Observed ceftaroline concentrations (mcg/mL) are plotted versus individual predictions by age group. Values are indicated by open circles. The line of identity (solid black) is included as a reference. The age group is listed at the top of each plot.



Adapted from the Sponsor's report of Study CPT-MS-08, Figure 44

As requested by the Agency, the Sponsor summarized model parameter estimates by age groups. Please refer to Tables 14, 15, 16, 17, and 18 for detail.

Reviewer's Comment: Based on the reported reduction of the objective function of NONMEM and the visual examination of plots of observed versus predicted plasma ceftaroline concention

in different age groups, the quality of fit of the pharmacokinetic model to the data seems acceptable.

Table 14 Summary of PK Parameters for 28d-<2yr Patients

parameter	N	minimum	maximum	median	mean	%CV
CLcf (L/h)	64	9.9600	172.00	54.500	61.100	53
Vccf (L)	64	0.0988	8.18	1.170	1.500	95
Q1cf (L/h)	64	3.2400	7.19	5.580	5.580	17
Vp1cf (L)	64	0.4430	1.28	0.916	0.922	23
K14 ($1/hr$)	64	2.0100	1710.00	49.200	96.700	220
CLc (L/h)	64	0.5700	3.93	1.810	1.920	37
Vcc (L)	64	0.8720	6.24	2.260	2.520	38
Qc (L/h)	64	1.1000	2.44	1.890	1.890	17
Vpc (L)	64	0.6350	1.90	1.370	1.370	23

CLcf = clearance ceft fos, Vccf = central volume ceft fos, Q1cf = intercompartmental clearance ceft fos, Vp1cf = peripheral volume ceft fos, K14 = rate constant for conversion of ceft fos to ceftaroline, CLc = clearance ceftaroline, Vcc = central volume ceftaroline, Qc = intercompartmental clearance ceftaroline, Vpc = peripheral volume ceftaroline, %CV = percent coefficient of variation.

Adapted from the Sponsor's report of Study CPT-MS-08-ppktables (response to IR, SDN498), Table 3

Table 15 Summary of PK Parameters for 2-<6yr Patients

parameter	N	minimum	maximum	median	mean	%CV
CLcf (L/h)	102	4.910	262.00	81.70	90.10	53
Vccf (L)	102	0.733	128.00	2.10	5.32	270
Q1cf (L/h)	102	5.630	14.20	8.52	8.60	19
Vp1cf (L)	102	0.926	3.18	1.61	1.64	26
K14 ($1/hr$)	102	0.398	245.00	42.60	50.80	90
CLc (L/h)	102	1.400	7.04	3.44	3.54	29
Vcc (L)	102	1.130	9.23	3.64	4.01	38
Qc (L/h)	102	1.910	4.82	2.89	2.92	19
Vpc (L)	102	1.410	4.79	2.36	2.44	26

CLcf = clearance ceft fos, Vccf = central volume ceft fos, Q1cf = intercompartmental clearance ceft fos, Vp1cf = peripheral volume ceft fos, K14 = rate constant for conversion of ceft fos to ceftaroline, CLc = clearance ceftaroline, Vcc = central volume ceftaroline, Qc = intercompartmental clearance ceftaroline, Vpc = peripheral volume ceftaroline, %CV = percent coefficient of variation.

Adapted from the Sponsor's report of Study CPT-MS-08-ppktables (response to IR, SDN498), Table 4

Table 16 Summary of PK Parameters for 6-<12yr Patients

parameter	N	minimum	maximum	median	mean	%CV
CLcf (L/h)	73	12.900	303.00	122.00	132.00	50
Vccf (L)	73	0.631	90.30	3.15	6.02	210
Q1cf (L/h)	73	7.060	26.60	12.60	13.60	30
Vp1cf (L)	73	1.250	7.33	2.71	3.07	41
K14 ($1/hr$)	73	0.481	480.00	44.90	57.80	110
CLc (L/h)	73	2.000	14.60	5.71	6.07	35
Vcc (L)	73	1.800	17.50	6.69	7.16	43
Qc (L/h)	73	2.400	9.01	4.27	4.62	30
Vpc (L)	73	1.900	10.90	4.04	4.52	41

CLcf = clearance ceft fos, Vccf = central volume ceft fos, Q1cf = intercompartmental clearance ceft fos, Vp1cf = peripheral volume ceft fos, K14 = rate constant for conversion of ceft fos to ceftaroline, CLc = clearance ceftaroline, Vcc = central volume ceftaroline, Qc = intercompartmental clearance ceftaroline, Vpc = peripheral volume ceftaroline, %CV = percent coefficient of variation.

Adapted from the Sponsor's report of Study CPT-MS-08-ppktables (response to IR, SDN498), Table 5

Table 17 Summary of PK Parameters for 12-<18yr Patients

parameter	N	minimum	maximum	median	mean	%CV
CLcf (L/h)	42	24.30	776.00	198.00	219.00	67
Vccf (L)	42	1.92	52.10	5.65	8.50	110
Q1cf (L/h)	42	9.72	32.60	21.60	22.00	21
Vp1cf (L)	42	1.92	9.64	5.55	5.75	28
K14 ($1/hr$)	42	1.71	403.00	33.80	48.90	140
CLc (L/h)	42	2.47	15.10	8.89	9.34	31
Vcc (L)	42	3.55	30.20	12.20	13.00	44
Qc (L/h)	42	3.30	11.10	7.32	7.45	21
Vpc (L)	42	2.96	14.30	8.15	8.52	28

CLcf = clearance ceft fos, Vccf = central volume ceft fos, Q1cf = intercompartmental clearance ceft fos, Vp1cf = peripheral volume ceft fos, K14 = rate constant for conversion of ceft fos to ceftaroline, CLc = clearance ceftaroline, Vcc = central volume ceftaroline, Qc = intercompartmental clearance ceftaroline, Vpc = peripheral volume ceftaroline, %CV = percent coefficient of variation.

Adapted from the Sponsor's report of Study CPT-MS-08-ppktables (response to IR, SDN498), Table 6

Table 18 Summary of PK Parameters for Adult Patients

parameter	N	minimum	maximum	median	mean	%CV
CLcf (L/h)	220	26.1000	921.0	259.00	297.00	51
Vccf (L)	220	1.4500	787.0	6.71	12.70	420
Q1cf (L/h)	220	16.4000	40.6	26.00	26.30	16
Vp1cf (L)	220	3.8600	12.9	7.13	7.29	22
K14 ($1/hr$)	220	0.0986	448.0	39.70	57.80	100
CLc (L/h)	220	2.4200	28.1	9.48	10.00	37
Vcc (L)	220	5.6000	65.2	15.60	17.60	44
Qc (L/h)	220	5.5700	13.8	8.83	8.93	16
Vpc (L)	220	5.6500	20.2	10.40	10.70	22

CLcf = clearance ceft fos, Vccf = central volume ceft fos, Q1cf = intercompartmental clearance ceft fos, Vp1cf = peripheral volume ceft fos, K14 = rate constant for conversion of ceft fos to ceftaroline, CLc = clearance ceftaroline, Vcc = central volume ceftaroline, Qc = intercompartmental clearance ceftaroline, Vpc = peripheral volume ceftaroline, %CV = percent coefficient of variation.

Adapted from the Sponsor's report of Study CPT-MS-08-ppktables (response to IR, SDN498), Table 7

Reviewer's Comment: For ceftaroline, variance parameter estimates (%CV) for CLc, Vcc, Qc, and Vpc demonstrated a low to moderate degree of unexplained variability for age groups from 28 days and above. CLc and Vcc increased with the increase of age and weight. Values are more consistent after normalizing for body weight, supporting the inclusion of body weight in the model and the use of weight-based dosing. Please refer to the table below for additional details.

Age group	****CLc (L/h)***	****Vcc (L)***	****Weight (kg)***	****CLc (L/h/kg)***	****Vc (L/kg)***	***Proposed dose***	***Dose by weight***
adult	*9.48*	*15.6*	*74*	*0.13*	*0.21*	*600 mg q12hrs*	*8 mg/kg q12hrs*
12-<18 yrs	*8.89*	*12.2*	*51.5*	*0.17*	*0.24*	*12 mg/kg q8hrs*	*12 mg/kg q8hrs*
6-<12 yrs	*5.71*	*6.67*	*33.2*	*0.17*	*0.20*	*12 mg/kg q8hrs*	*12 mg/kg q8hrs*
2-<6 yrs	*3.44*	*3.64*	*20.4*	*0.17*	*0.18*	*12 mg/kg q8hrs*	*12 mg/kg q8hrs*
1m - <2 yrs	*1.81*	*2.26*	*9.2*	*0.20*	*0.25*	*8 mg/kg q8hrs*	*8 mg/kg q8hrs*

**Median value only*

4.6.5 Model Evaluation Results

The Sponsor reported that the ceftaroline population PK model evaluation results, which included the results of a predictive check and a non-parametric bootstrap, revealed that the final model provided a reliable description of the data with good precision of structural model and most variance parameter estimates.

The Reviewer's Comment: The reviewer did not repeat the Sponsor's model diagnostics. The provided diagnostic plots for the predictive check and non-parametric bootstrap support the conculsion that the final model provides a reasonable description of the data; however, there was difficulty in describing the central tendency of C_{max} in some age groups (12 to 18 years and 2 to 6 years). The Sponsor concludes that the model is acceptable for simulation and the reviewer concurs.

4.6.6 Exposure and Target Attainment Simulations Results

The final combined ceftaroline fosamil and ceftaroline population PK model (Run 118) was used for all simulations in this report to evaluate the weight based doses and 2 different infusion lengths (5 minutes and 1 hour) in pediatric patients from 2 months to <18 years old. The adult doses of 600 mg q12h following as a 1-hour infusion and 600 mg q12h as a 5-minute infusion were simulated for comparison to the results from pediatric patients. The adult exposure in a patient with normal renal function was used for all pediatric comparisons.

The simulation results for the pediatric patients with normal renal function and an infusion duration of 5 minutes for two dosing regimens, 8 mg/kg q8h and 12 mg/kg q8h, respectively, are in Table 19 and Table 20 below.

Table 19 Median (90% PI) Steady State Ceftaroline $C_{max,SS}$, $AUC_{24,SS}$, and %T>MIC by Age for Normal Renal Function Following 8 mg/kg (max of 400 mg) q8h Dosing (5 Minute Infusion) in Pediatric Patients Based on Simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 5min	77.6 (52.5,105)	26.5 (13.6,52.0)	97.5 (59.2,164)	60.5 (41.3,90.1)	42.1 (26.4,65.3)
12-<18 years	52.9 (36.8,75.3)	24.3 (12.8,44.8)	115 (72.3,180)	76.5 (51.9,100)	51.9 (33.3,79.1)
6-<12 years	28.5 (19.3,46.5)	26.2 (14.6,47.2)	111 (71.1,173)	69.1 (46.9,97.5)	48.1 (30.9,72.9)
2-<6 years	15.8 (11.8,22.2)	25.6 (14.2,46.5)	95.9 (61.8,149)	59.3 (40.7,85.2)	40.7 (27.2,61.7)
18-<24 months	11.7 (9.81,14.1)	26.3 (14.7,46.8)	107 (69.2,166)	66.7 (46.9,93.8)	46.9 (30.9,69.1)
12-<18 months	10.4 (8.60,12.7)	26.4 (14.9,47.5)	112 (71.9,174)	69.1 (48.1,96.3)	49.4 (32.1,72.8)
6-<12 months	8.43 (6.55,10.7)	26.6 (14.9,46.9)	121 (78.1,188)	75.3 (53.0,98.8)	53.1 (35.8,80.2)
2-<6 months	5.75 (4.12,7.66)	25.1 (14.4,44.0)	134 (86.5,209)	87.7 (60.5,100)	63.0 (42.0,92.6)
1-<2 months	4.69 (3.63,5.77)	23.5 (13.5,40.8)	139 (90.5,216)	93.8 (66.6,100)	67.9 (45.7,96.3)
0-<1 month	3.88 (2.91,4.75)	21.9 (12.8,37.6)	144 (93.6,221)	97.5 (71.6,100)	73.1 (49.4,98.8)
GA 38-<40 weeks	3.40 (2.55,4.24)	20.1 (12.0,33.9)	153 (98.8,234)	100 (81.5,100)	84.0 (56.7,100)
GA 36-<38 weeks	2.87 (2.07,3.75)	19.6 (11.6,33.3)	146 (94.5,226)	99.4 (77.8,100)	80.2 (53.1,100)
GA 34-<36 weeks	2.32 (1.71,3.05)	19.2 (11.2,32.8)	138 (89.2,214)	98.8 (74.1,100)	75.3 (50.6,98.8)
GA 32-<34 weeks	1.89 (1.38,2.44)	19.0 (11.1,32.8)	131 (85.0,202)	96.6 (69.1,100)	71.3 (48.1,97.5)
GA 30-<32 weeks	1.50 (1.05,1.95)	18.7 (10.8,32.2)	123 (79.7,191)	92.6 (65.4,100)	66.0 (44.4,95.1)
GA 28-<30 weeks	1.15 (0.779,1.52)	18.3 (10.7,31.9)	116 (74.6,179)	87.7 (60.5,100)	61.7 (40.7,90.2)

median(5^{th},95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).
Adult dose and regimen is listed in first row of column 1.

Adapted from the Sponsor's report of Study CPT-MS-08-Ceftaroline Pediatric Dosing Regimen Simulation (response to IR, SDN505), Table 17

Table 20 Median (90% PI) Steady State Ceftaroline $C_{max,SS}$, $AUC_{24,SS}$, and %T>MIC by Age for Normal Renal Function Following 12 mg/kg (max of 400 mg) q8h Dosing (5 Minute Infusion) to in Pediatric Patients Based on Simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 5min	77.6 (52.5,105)	26.5 (13.8,52.0)	97.2 (58.6,164)	60.3 (41.3,90.1)	42.1 (26.4,65.3)
12-<18 years	52.9 (36.8,75.3)	25.7 (13.1,50.7)	122 (73.8,203)	79.0 (53.1,100)	54.3 (34.6,84.0)
6-<12 years	28.5 (19.3,46.5)	37.4 (20.0,69.2)	157 (99.7,247)	79.0 (55.6,100)	58.0 (39.5,86.4)
2-<6 years	15.8 (11.8,22.2)	38.4 (21.2,68.7)	144 (92.2,222)	70.4 (49.3,97.5)	51.9 (34.6,75.3)
18-<24 months	11.7 (9.81,14.1)	39.6 (22.1,71.3)	161 (104,248)	77.8 (54.3,100)	58.0 (39.5,84.0)
12-<18 months	10.4 (8.60,12.7)	39.7 (22.1,70.9)	169 (108,261)	81.5 (56.8,100)	60.5 (42.0,88.9)
6-<12 months	8.43 (6.55,10.7)	39.7 (22.5,71.8)	182 (117,282)	88.0 (61.7,100)	66.7 (45.7,95.1)
2-<6 months	5.75 (4.12,7.66)	37.6 (21.2,66.6)	201 (130,311)	97.5 (71.6,100)	77.8 (53.1,100)
1-<2 months	4.69 (3.63,5.77)	35.6 (20.4,61.7)	211 (137,326)	100 (77.7,100)	84.0 (58.0,100)
0-<1 month	3.88 (2.91,4.75)	32.8 (19.0,57.0)	215 (140,330)	100 (84.0,100)	90.1 (62.9,100)
GA 38-<40 weeks	3.40 (2.55,4.24)	29.9 (17.6,50.8)	228 (149,349)	100 (95.1,100)	97.5 (71.6,100)
GA 36-<38 weeks	2.87 (2.07,3.75)	29.5 (17.5,50.8)	218 (142,339)	100 (91.4,100)	96.3 (67.9,100)
GA 34-<36 weeks	2.32 (1.71,3.05)	29.0 (17.2,49.6)	208 (134,321)	100 (87.7,100)	92.6 (64.2,100)
GA 32-<34 weeks	1.89 (1.38,2.44)	28.4 (16.8,48.9)	197 (126,307)	100 (82.7,100)	87.7 (60.5,100)
GA 30-<32 weeks	1.50 (1.05,1.95)	28.0 (16.3,48.1)	186 (121,285)	100 (77.8,100)	82.7 (56.8,100)
GA 28-<30 weeks	1.15 (0.779,1.52)	27.5 (15.9,48.0)	173 (113,268)	98.1 (71.6,100)	76.5 (53.0,98.8)

median(5^{th},95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).

Adult dose and regimen is listed in first row of column 1.

Adapted from the Sponsor's report of Study CPT-MS-08-Ceftaroline Pediatric Dosing Regimen Simulation (response to IR, SDN505), Table 25

For patients with normal renal function, simulations predict that the proposed dose regimen of 8 mg/kg q8h as a 5 mintues infusion will result in 99.7-100% of the patients age 2 months to < 2 years achieving the PK/PD target associated with 1-log kill of *S aureus* (36% fT>MIC, MIC = 1 mg/L). Similarly, 100% of such patients are predicted to achieve the PK/PD target associated with 1-log kill of *S. pneumonia* (44% fT>MIC, MIC = 0.5 mg/L). For the propsed dose regiment of 12 mg/kg q8h as a 5 minute infusion, 100% of the patients age 2 to < 18 years are predicted to achieve PK/PD target associated with 1-log kill of *S aureus* (36% fT>MIC, MIC = 1 mg/L) and 100% of the patients are predicted to achieve the PK/PD target associated with 1-log kill of *S. pneumonia* (44% fT>MIC, MIC = 0.5 mg/L).

Reviewer's Comment: Based on the simulation results, with proposed doses, the estimates of median $C_{max,ss}$ for patients age 2 to 24 months were similar ($C_{max,ss}$ ratio 0.946-1.01) to adults with normal renal function receiving a 5 minute infusion. For the same age group, the $AUC_{24,ss}$ were slightly higher ($AUC_{24,ss}$ ratio 1.10-1.37) compared to adults. The 90% PI also indicated same trend for both $C_{max,s}$s and $AUC_{24,ss}$.

With the proposed dose (12 mg/kg every 8 hours up to 400 mg for 33 kg), the estimates of median $C_{max,ss}$ for patients age 2 to 12 years were higher (median $C_{max,ss}$ ratio 1.41 to 1.45) compared to the adults with normal renal function receiving 5 minutes infusion. In contrast, $C_{max,ss}$ for patients age 12 to 18 years was similar (median $C_{max,ss}$ ration 0.97) to the adults. For the patients age 2 to <18 years, the $AUC_{24,ss}$ were higher (median $AUC_{24,ss}$ ratio 1.26 to 1.61) compared to adults. The 90% PI also indicated same trend for both $C_{max,ss}$ and $AUC_{24,ss}$.

Target attainment stimulation results in Table 19 and 20 indicated that the median percent of time to dosing interval for free ceftaroline over MIC for MIC of 1 mg/L was higher in pediatric patients with proposed dose compared to adults (66.7% to 87.7% for patients age 2 months to 18 years compared to 60.5% for adults).

The simulation results for the pediatric patients with mild renal impairment for the duration of infusion of 5 minutes for two dosing regimens, 8 mg/kg q8h and 12 mg/kg q8h, respectively, are in Table 21 and Table 22 below.

Table 21 Median (90% PI) Steady State Ceftaroline $C_{max,SS}$, $AUC_{24,SS}$, and %T>MIC by Age for Mild Renal Impairment Following 8 mg/kg (max of 400 mg) q8h Dosing (5 Minute Infusion) in Pediatric Patients Based on Simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 5 min	77.6 (52.2,105)	26.5 (13.6,52.3)	96.9 (58.8,164)	60.3 (41.3,90.1)	42.1 (26.4,65.3)
12-<18 years	52.7 (36.7,74.7)	25.0 (13.4,46.0)	128 (79.8,204)	85.2 (58.0,100)	59.3 (37.6,91.4)
6-<12 years	28.6 (19.2,46.8)	26.9 (15.0,48.3)	123 (77.5,193)	76.5 (51.9,100)	54.3 (34.6,84.0)
2-<6 years	15.8 (11.8,22.4)	26.2 (14.6,46.4)	107 (67.6,166)	65.4 (44.4,95.1)	45.7 (29.6,69.2)
18-<24 months	11.7 (9.82,14.1)	27.6 (15.5,49.6)	133 (82.6,218)	82.7 (54.3,100)	59.3 (37.0,93.8)
12-<18 months	10.4 (8.58,12.7)	27.7 (15.6,49.1)	140 (85.9,228)	87.7 (57.4,100)	63.0 (39.5,96.3)
6-<12 months	8.43 (6.56,10.8)	27.9 (16.0,49.7)	152 (92.6,247)	93.8 (61.7,100)	69.1 (43.2,98.8)
2-<6 months	5.75 (4.11,7.67)	26.6 (15.3,46.5)	168 (104,275)	98.8 (71.6,100)	80.2 (50.6,100)
1-<2 months	4.69 (3.63,5.77)	25.3 (14.8,43.7)	175 (108,285)	100 (77.8,100)	87.3 (55.5,100)
0-<1 month	3.86 (2.91,4.75)	23.6 (14.0,40.2)	179 (111,292)	100 (85.2,100)	92.6 (59.8,100)
GA 38-<40 weeks	3.40 (2.56,4.26)	21.8 (13.0,36.4)	191 (117,307)	100 (95.1,100)	97.5 (69.1,100)
GA 36-<38 weeks	2.86 (2.06,3.77)	21.4 (12.8,36.2)	181 (112,295)	100 (92.5,100)	96.6 (64.2,100)
GA 34-<36 weeks	2.33 (1.73,3.06)	21.1 (12.6,35.3)	174 (107,280)	100 (87.7,100)	95.1 (61.7,100)
GA 32-<34 weeks	1.89 (1.38,2.44)	20.6 (12.1,34.6)	164 (101,270)	100 (84.0,100)	91.4 (57.4,100)
GA 30-<32 weeks	1.50 (1.06,1.95)	20.1 (11.8,34.1)	155 (96.0,251)	100 (79.0,100)	85.2 (53.1,100)
GA 28-<30 weeks	1.16 (0.779,1.53)	19.6 (11.6,33.8)	145 (89.4,236)	98.8 (72.8,100)	79.0 (49.4,100)

median(5^{th},95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).

Adult dose and regimen is listed in first row of column 1.

Adapted from the Sponsor's report of Study CPT-MS-08-Ceftaroline Pediatric Dosing Regimen Simulation (response to IR, SDN505), Table 49

Table 22 Median (90% PI) Steady State Ceftaroline $C_{max,SS}$, $AUC_{24,SS}$, and %T>MIC by Age for Mild Renal Impairment Following 12 mg/kg (max of 400 mg) q8h Dosing (5 Minute Infusion) in Pediatric Patients Based on Simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 5 min	77.6 (52.2,105)	26.5 (13.6,52.3)	96.9 (58.8,164)	60.3 (41.3,90.1)	42.1 (26.4,65.3)
12-<18 years	52.7 (36.7,74.7)	26.5 (13.7,51.2)	136 (81.6,226)	87.7 (59.3,100)	61.7 (38.3,93.8)
6-<12 years	28.6 (19.2,46.8)	38.2 (20.5,69.8)	175 (109,276)	88.6 (60.5,100)	65.4 (43.2,95.1)
2-<6 years	15.8 (11.8,22.4)	39.3 (22.0,69.6)	160 (101,249)	77.8 (53.1,100)	58.0 (38.3,85.2)
18-<24 months	11.7 (9.82,14.1)	41.5 (23.3,74.4)	200 (124,327)	95.1 (64.2,100)	72.8 (46.9,100)
12-<18 months	10.4 (8.58,12.7)	41.6 (23.4,73.6)	210 (129,341)	97.5 (67.9,100)	76.5 (50.6,100)
6-<12 months	8.43 (6.56,10.8)	41.9 (24.1,74.6)	228 (139,371)	100 (72.8,100)	84.6 (54.3,100)
2-<6 months	5.75 (4.11,7.67)	39.9 (22.9,69.7)	252 (156,412)	100 (84.0,100)	95.1 (63.0,100)
1-<2 months	4.69 (3.63,5.77)	37.9 (22.2,65.5)	262 (162,427)	100 (91.4,100)	98.8 (69.1,100)
0-<1 month	3.86 (2.91,4.75)	35.3 (21.0,60.3)	269 (166,438)	100 (97.5,100)	100 (74.7,100)
GA 38-<40 weeks	3.40 (2.56,4.26)	32.8 (19.5,54.5)	286 (176,461)	100 (100,100)	100 (85.2,100)
GA 36-<38 weeks	2.86 (2.06,3.77)	32.1 (19.2,54.3)	272 (169,442)	100 (98.8,100)	100 (81.4,100)
GA 34-<36 weeks	2.33 (1.73,3.06)	31.6 (18.8,52.9)	260 (161,421)	100 (97.5,100)	100 (77.7,100)
GA 32-<34 weeks	1.89 (1.38,2.44)	30.9 (18.2,52.0)	246 (151,405)	100 (96.3,100)	98.8 (72.8,100)
GA 30-<32 weeks	1.50 (1.06,1.95)	30.1 (17.8,51.2)	233 (144,376)	100 (91.4,100)	97.5 (67.9,100)
GA 28-<30 weeks	1.16 (0.779,1.53)	29.4 (17.3,50.7)	217 (134,355)	100 (85.8,100)	95.1 (63.0,100)

median(5^{th},95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).
Adult dose and regimen is listed in first row of column 1.

Adapted from the Sponsor's report of Study CPT-MS-08-Ceftaroline Pediatric Dosing Regimen Simulation (response to IR, SDN505), Table 57

For patients with mild renal impairment, the simulation results indicated 100% of the patients age 2 months to < 18 years were predicted to achieve the PK/PD target associated with 1-log kill of *S aureus* (36% fT>MIC, MIC = 1 mg/L) and 1-log kill of *S. pneumonia* (44% fT>MIC, MIC = 0.5 mg/L) with the proposed dose regimen following 5 minutes IV infusion.

Reviewer's Comment: Based on the simulation results with proposed dose (8mg/kg every 8 hours), the estimates of median (90% PI) $C_{max,ss}$ for patients age 2 to 24 months were similar (median $C_{max,ss}$ ratio 1.01 to 1.04) to the adults with normal renal function receiving a 5 minute infusion. For the same age group, the median (90% PI) $AUC_{24,ss}$ were higher ($AUC_{24,ss}$ ratio 1.37 to 1.73) compared to adults.

With the proposed dose (12 mg/kg every 8 hours up to 400 mg for 33 kg), the estimates of median (90% CI) $C_{max,ss}$ for patients age 2 to 12 years were higher (median $C_{max,ss}$ ratio 1.45 to 1.48) compared to the adults with normal renal function receiving a 5 minute infusion. In contrast, $C_{max,ss}$ for patients age 12 to 18 years was similar (median $C_{max,ss}$ ration 1.00) to the adults. For the patients age 2 to 18 years, the median (90% PI) $AUC_{24,ss}$ were higher (median $AUC_{24,ss}$ ratio 1.40 to 1.80) compared to adults.

Target attainment stimulation results in Table 21 and 22 indicated that the median percent time of the dosing interval free ceftaroline exceeds MIC (%fT>MIC) for MIC of 1 mg/L was higher in

pediatric patients with the proposed dose compared to adults (77.8% to 98.8% for patients age 2 months to 18 years compared to 60.5% for adults), especially for patients age 2 to 12 months (93.8%-98.8%).

The simulation results for the pediatric patients with normal renal function and a 1 hour infusion for the two dosing regimens 8 mg/kg q8h and 12 mg/kg q8h, respectively, are in Table 23 and Table 24 below.

Table 23 Median (90% PI) Steady State Ceftaroline $C_{max,SS}$, $AUC_{24,SS}$, and %T>MIC by Age for Normal Renal Function Following 8 mg/kg (max of 400 mg) q8h Dosing (1 Hour Infusion) in Pediatric Patients Based on Simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	20.8 (11.7,36.4)	97.5 (59.1,164)	64.5 (45.0,93.4)	45.0 (29.8,68.7)
12-<18 years	52.9 (36.8,75.3)	18.7 (10.9,30.0)	115 (72.2,179)	82.7 (58.0,100)	56.8 (38.3,85.2)
6-<12 years	28.5 (19.3,46.5)	19.3 (11.9,30.2)	111 (71.0,173)	74.1 (53.0,98.8)	53.1 (35.8,78.4)
2-<6 years	15.8 (11.8,22.2)	18.0 (11.2,27.6)	95.7 (62.0,148)	64.2 (46.9,91.4)	45.7 (32.0,66.7)
18-<24 months	11.7 (9.81,14.1)	18.8 (11.8,29.1)	107 (69.0,165)	71.9 (51.9,97.5)	51.9 (35.8,75.3)
12-<18 months	10.4 (8.60,12.7)	19.1 (11.9,29.4)	113 (71.8,174)	75.3 (54.3,98.8)	54.3 (37.0,77.8)
6-<12 months	8.43 (6.55,10.7)	19.6 (12.2,30.0)	120 (78.3,188)	80.2 (58.0,100)	59.3 (40.7,85.2)
2-<6 months	5.75 (4.12,7.66)	19.2 (12.1,29.7)	134 (86.6,208)	92.6 (66.7,100)	67.9 (46.9,96.3)
1-<2 months	4.69 (3.63,5.77)	18.6 (11.5,29.0)	139 (91.0,216)	97.2 (71.6,100)	72.8 (50.6,97.6)
0-<1 month	3.88 (2.91,4.75)	17.8 (11.1,27.7)	144 (93.3,223)	98.8 (77.7,100)	79.0 (54.3,99.4)
GA 38-<40 weeks	3.40 (2.55,4.24)	17.1 (10.6,26.5)	153 (98.6,234)	100 (87.6,100)	88.9 (60.5,100)
GA 36-<38 weeks	2.87 (2.07,3.75)	16.6 (10.3,25.9)	146 (94.9,226)	100 (83.9,100)	85.8 (58.0,100)
GA 34-<36 weeks	2.32 (1.71,3.05)	16.2 (10.0,25.2)	138 (89.3,214)	100 (80.2,100)	81.5 (54.3,100)
GA 32-<34 weeks	1.89 (1.38,2.44)	15.6 (9.87,24.4)	131 (85.3,202)	98.8 (75.3,100)	76.5 (51.9,98.8)
GA 30-<32 weeks	1.50 (1.05,1.95)	15.3 (9.41,24.1)	123 (79.9,191)	96.3 (70.4,100)	71.6 (48.1,97.5)
GA 28-<30 weeks	1.15 (0.779,1.52)	14.8 (9.18,23.2)	116 (74.9,179)	92.6 (66.7,100)	66.7 (45.7,93.9)

median(5^{th},95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).
Adult dose and regimen is listed in first row of column 1.

Adapted from the Sponsor's report of Study CPT-MS-08, Table 69

Table 24 Median (90% PI) Steady State Ceftaroline $C_{max,SS}$, $AUC_{24,SS}$, and %T>MIC by Age for Normal Renal Function Following 12 mg/kg (max of 400 mg) q8h Dosing (1 Hour Infusion) in Pediatric Patients Based on Simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.5,105)	21.0 (11.9,36.5)	97.3 (59.1,164)	64.0 (44.6,93.4)	45.0 (29.8,68.6)
12-<18 years	52.9 (36.8,75.3)	19.7 (11.0,34.2)	122 (72.7,201)	84.0 (59.3,100)	59.3 (38.9,88.9)
6-<12 years	28.5 (19.3,46.5)	27.6 (16.4,43.3)	157 (99.7,245)	85.2 (61.7,100)	63.0 (44.4,91.4)
2-<6 years	15.8 (11.8,22.2)	27.1 (16.8,41.8)	144 (92.6,225)	75.3 (54.3,98.8)	56.8 (40.7,81.5)
18-<24 months	11.7 (9.81,14.1)	28.3 (17.6,43.4)	160 (104,247)	82.7 (60.5,100)	63.0 (45.6,88.9)
12-<18 months	10.4 (8.60,12.7)	28.7 (17.9,44.0)	168 (109,260)	86.7 (63.0,100)	66.7 (47.5,92.7)
6-<12 months	8.43 (6.55,10.7)	29.3 (18.2,45.1)	182 (116,282)	93.2 (67.9,100)	71.6 (50.6,97.5)
2-<6 months	5.75 (4.12,7.66)	28.8 (17.9,44.6)	201 (130,310)	98.8 (77.7,100)	82.7 (59.2,100)
1-<2 months	4.69 (3.63,5.77)	28.0 (17.4,43.3)	210 (135,322)	100 (83.8,100)	88.9 (63.0,100)
0-<1 month	3.88 (2.91,4.75)	26.9 (16.8,41.9)	216 (140,333)	100 (90.1,100)	94.4 (67.9,100)
GA 38-<40 weeks	3.40 (2.55,4.24)	25.6 (15.8,39.9)	229 (149,355)	100 (97.5,100)	98.8 (77.7,100)
GA 36-<38 weeks	2.87 (2.07,3.75)	25.0 (15.5,39.3)	219 (141,338)	100 (96.3,100)	97.5 (74.0,100)
GA 34-<36 weeks	2.32 (1.71,3.05)	24.2 (15.2,38.1)	208 (136,321)	100 (93.8,100)	96.3 (70.4,100)
GA 32-<34 weeks	1.89 (1.38,2.44)	23.6 (14.8,37.3)	197 (128,305)	100 (88.9,100)	92.6 (66.7,100)
GA 30-<32 weeks	1.50 (1.05,1.95)	23.0 (14.1,36.0)	185 (119,287)	100 (83.3,100)	87.7 (61.7,100)
GA 28-<30 weeks	1.15 (0.779,1.52)	22.2 (13.8,34.8)	173 (113,269)	99.1 (78.9,100)	82.7 (58.0,100)

median(5^{th},95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).
Adult dose and regimen is listed in first row of column 1.

Adapted from the Sponsor's report of Study CPT-MS-08, Table 77

For patients with normal renal function, based on simulations for the proposed dose regimen and 1 hour infusion, 100% of the patients age 2 months to < 18 years are predicted to achieve PK/PD target associated with 1-log kill of *S aureus* (36% fT>MIC, MIC = 1 mg/L) and the PK/PD target associated with 1-log kill of *S. pneumonia* (44% fT>MIC, MIC = 0.5 mg/L).

Reviewer's Comment: Based on the simulation results, with proposed dose (8mg/kg q8h), the estimates of median (90% PI) $C_{max,ss}$ for patients age 2 to 24 months were similar (median $C_{max,ss}$ ratio 0.904 to 0.941) to the adults with normal renal function receiving 1 hour infusion. For the same age group, the median (90% CI) $AUC_{24,ss}$ were slightly higher ($AUC_{24,ss}$ ratio 1.10 to 1.37) compared to adults.

With the proposed dose (12 mg/kg q8h up to 400 mg for 33 kg), the estimates of median (90% PI) $C_{max,ss}$ for patients age 12 to 18 years were similar (median Cmax,ss ratio 0.935) to the adults with normal renal function receiving 1 hour infusion. The $C_{max,ss}$ of patients age 2 to 12 years were slightly higher (median $C_{max,ss}$ ratio 1.29 to 1.31) than exposures in adults. For patients age 2 to 18 years, the median (90% PI) $AUC_{24,ss}$ were higher (median $AUC_{24,ss}$ ratio 1.250 to 1.62) compared to the ones of adults.

Target attainment stimulation results in Table 23 and 24 indicated that the %fT>MIC for MIC of 1 mg/L was higher in pediatric patients with proposed dose compared to adults (71.9% to 92.6% for patients age 2 months to 18 years compared to 64.5% for adults).

The simulation results for the pediatric patients with mild renal impairment for the duration of infusion of 1 hour for two dosing regimens, 8 mg/kg q8h and 12 mg/kg q8h, respectively, are in Table 25 and Table 26 below.

Table 25 Median (90% PI) Steady State Ceftaroline $C_{max,SS}$, $AUC_{24,SS}$, %T>MIC by Age for Mild Renal Impairment Following 8 mg/kg (max of 400 mg) q8h Dosing (1 Hour Infusion) in Pediatric Patients Based on Simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.2,105)	20.9 (11.7,36.6)	97.1 (58.8,164)	64.5 (44.6,93.4)	45.5 (29.8,68.6)
12-<18 years	52.7 (36.7,74.7)	19.5 (11.5,31.5)	128 (79.4,203)	91.4 (64.1,100)	64.2 (42.0,95.1)
6-<12 years	28.6 (19.2,46.8)	20.3 (12.4,31.4)	123 (77.7,193)	82.7 (58.0,100)	59.3 (39.5,88.9)
2-<6 years	15.8 (11.8,22.4)	18.9 (11.8,28.9)	107 (67.7,166)	71.6 (50.6,97.5)	50.6 (34.6,75.3)
18-<24 months	11.7 (9.82,14.1)	20.6 (12.8,32.3)	133 (82.7,219)	88.9 (60.5,100)	64.8 (42.0,96.3)
12-<18 months	10.4 (8.58,12.7)	20.9 (13.0,32.6)	140 (86.0,227)	92.6 (63.0,100)	67.9 (44.4,98.8)
6-<12 months	8.43 (6.56,10.8)	21.4 (13.3,33.3)	152 (92.6,247)	97.5 (67.9,100)	75.3 (48.1,100)
2-<6 months	5.75 (4.11,7.67)	21.2 (13.2,33.3)	168 (103,275)	100 (77.8,100)	86.4 (55.6,100)
1-<2 months	4.69 (3.63,5.77)	20.6 (12.8,32.3)	175 (108,284)	100 (84.0,100)	91.7 (60.5,100)
0-<1 month	3.86 (2.91,4.75)	19.8 (12.3,31.4)	179 (111,292)	100 (91.3,100)	96.3 (65.4,100)
GA 38-<40 weeks	3.40 (2.56,4.26)	19.1 (11.7,30.1)	191 (117,307)	100 (97.5,100)	98.8 (74.0,100)
GA 36-<38 weeks	2.86 (2.06,3.77)	18.5 (11.5,29.2)	181 (112,294)	100 (96.2,100)	98.8 (69.1,100)
GA 34-<36 weeks	2.33 (1.73,3.06)	18.1 (11.3,28.7)	173 (107,281)	100 (93.2,100)	96.3 (66.6,100)
GA 32-<34 weeks	1.89 (1.38,2.44)	17.5 (10.9,27.8)	164 (101,270)	100 (88.9,100)	95.1 (62.9,100)
GA 30-<32 weeks	1.50 (1.06,1.95)	17.0 (10.6,26.9)	155 (96.2,251)	100 (84.0,100)	90.1 (58.6,100)
GA 28-<30 weeks	1.16 (0.779,1.53)	16.4 (10.2,25.9)	145 (89.3,237)	100 (79.0,100)	85.2 (54.3,100)

median(5^{th},95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).
Adult dose and regimen is listed in first row of column 1.

Adapted from the Sponsor's report of Study CPT-MS-08, Table 141

Table 26 Median (90% PI) Steady State Ceftaroline $C_{max,SS}$, $AUC_{24,SS}$, %T>MIC by Age for Mild Renal Impairment Following 12 mg/kg (max of 400 mg) q8h Dosing (1 Hour Infusion) in Pediatric Patients Based on Simulations

AGE	Weight (kg)	CmaxSS (mg/L)	AUC24SS (mg*hr/L)	%T>MIC of 1 mg/L	%T>MIC of 2 mg/L
Adults 600 mg q12h 1 hr	77.6 (52.2,105)	20.9 (11.9,36.4)	97.3 (59.0,164)	64.5 (44.6,93.4)	44.6 (29.8,68.6)
12-<18 years	52.7 (36.7,74.7)	20.7 (11.5,35.6)	136 (80.9,227)	92.6 (65.4,100)	66.7 (43.2,96.3)
6-<12 years	28.6 (19.2,46.8)	28.8 (17.0,45.4)	175 (110,276)	93.8 (66.7,100)	70.4 (48.1,97.5)
2-<6 years	15.8 (11.8,22.4)	28.3 (17.5,44.0)	160 (102,252)	82.7 (59.3,100)	63.0 (44.4,90.2)
18-<24 months	11.7 (9.82,14.1)	31.0 (19.1,47.9)	201 (124,325)	98.8 (70.4,100)	79.0 (53.1,100)
12-<18 months	10.4 (8.58,12.7)	31.5 (19.5,48.9)	210 (130,343)	98.8 (72.8,100)	82.7 (55.6,100)
6-<12 months	8.43 (6.56,10.8)	32.2 (20.0,49.9)	227 (140,370)	100 (79.0,100)	90.1 (60.5,100)
2-<6 months	5.75 (4.11,7.67)	31.7 (19.6,49.6)	252 (155,409)	100 (90.1,100)	97.5 (69.1,100)
1-<2 months	4.69 (3.63,5.77)	31.0 (19.1,48.3)	262 (161,424)	100 (96.2,100)	98.8 (74.1,100)
0-<1 month	3.86 (2.91,4.75)	29.8 (18.5,46.9)	269 (167,436)	100 (98.8,100)	100 (80.2,100)
GA 38-<40 weeks	3.40 (2.56,4.26)	28.6 (17.6,45.5)	286 (177,465)	100 (100,100)	100 (91.3,100)
GA 36-<38 weeks	2.86 (2.06,3.77)	27.9 (17.1,44.1)	273 (168,445)	100 (100,100)	100 (86.4,100)
GA 34-<36 weeks	2.33 (1.73,3.06)	27.0 (16.9,42.7)	259 (161,420)	100 (98.8,100)	100 (83.9,100)
GA 32-<34 weeks	1.89 (1.38,2.44)	26.3 (16.3,41.7)	246 (152,403)	100 (98.7,100)	100 (78.4,100)
GA 30-<32 weeks	1.50 (1.06,1.95)	25.5 (15.7,40.2)	232 (144,378)	100 (96.2,100)	98.8 (74.0,100)
GA 28-<30 weeks	1.16 (0.779,1.53)	24.5 (15.1,39.1)	217 (133,355)	100 (91.2,100)	97.5 (67.9,100)

median(5^{th},95^{th}) based on summary of 100 trials and corresponds to median(90% prediction interval).
Adult dose and regimen is listed in first row of column 1.

Adapted from the Sponsor's report of Study CPT-MS-08, Table 149

For patients with mild renal impairment, based on simulations for the proposed dose regimen following 1 hour infusion, 100% of the patients age 2 months to < 18 years are predicted to achieve PK/PD target associated with 1-log kill of *S aureus* (36% fT>MIC, MIC = 1 mg/L) and the PK/PD target associated with 1-log kill of *S. pneumonia* (44% fT>MIC, MIC = 0.5 mg/L).

Reviewer's Comment: Based on the simulation results, with proposed dose (8mg/kg q8h, the estimates of median (90% PI) $C_{max,ss}$ for patients age 2 to 24 months were similar (median $C_{max,ss}$ ratio 0.99 to 1.03) to adults with normal renal function receiving 1 hour infusion. For the same age group, the median (90% PI) $AUC_{24,ss}$ were higher ($AUC_{24,ss}$ ratio 1.37 to 1.73) compared to adults.

With the proposed dose (12 mg/kg q8h up to 400 mg for 33 kg), the estimates of median (90% PI) $C_{max,ss}$ for patients age 12 to 18 years were similar (median $C_{max,ss}$ ratio 0.992) to the adults with normal renal function receiving 1 hour infusion. The $C_{max,ss}$ of patients age 2 to 12 years were slightly higher (median $C_{max,ss}$ ratio 1.35 to 1.38) than these of adults. For patients age 2 to 18 years, the median (90% PI) $AUC_{24,ss}$ were higher (median $AUC_{24,ss}$ ratio 1.40 to 1.64) compared to the ones of adults.

Target attainment stimulation results in Table 25 and 26 indicated that the %fT>MIC for MIC of 1 mg/L was higher in pediatric patients with proposed dose compared to adults (82.7% to 100% for patients age 2 months to 18 years compared to 64.5% for adults).

Due to the limited amount of clinical data in pediatric patients with renal impairment, especially patients with moderate or severe renal impairment, it is reasonable not to propose any dosing regimens for this sub-population.

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/s/

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05/10/2016

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