CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200327

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 200-327	Submission Date(s): • 30 Dec 2009 (SDN 1) • 04 Feb 2010 (SDN 7) • 23 Apr 2010 (SDN 10) • 29 Apr 2010 (SDN 13) • 30 Apr 2010 (SDN 14) • 18 Jun 2010 (SDN 19) • 06 Aug 2010 (SDN 31) • 18 Aug 2010 (SDN 34)
Drug	Ceftaroline Fosamil for Injection
Trade Name	TEFLARO™ (proposed)
OCP Reviewer	Aryun Kim, Pharm.D.
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OCP Division	DCP4
OND division	DAIOP (520)
Sponsor	Cerexa, Inc., Oakland, CA
Relevant IND(s)	IND 71,371
Submission Type; Code	Original New Drug Application (New Molecular Entity), 1S
Formulation; Strength(s)	Sterile (b) (4) of ceftaroline fosamil and L-arginine supplied as powder in single-use, 20-cc, clear, Type I glass vials containing 600 mg or 400 mg of ceftaroline fosamil
Indication	For the treatment of complicated skin and skin structure infections (cSSSI) and community-acquired bacterial pneumonia (CABP) caused by designated susceptible isolates of Gram-positive and Gram-negative microorganisms
Dosage and Administration	600 mg administered every 12 hours by intravenous infusion over 1 hour in patients ≥18 years of age • for 5-14 days for treatment of cSSSI • for 5-7 days for treatment of CABP

Abbreviations

Ae, cumulative amount excreted in urine
AUC, area under plasma concentration-time curve
AUC_{24}, area under plasma concentration-time curve over 24 hours
AUC_{inf}, area under plasma concentration-time curve from time 0 to infinity
AUC_{tau}, area under plasma concentration-time curve over dosing interval
AZT, aztreonam
C_{max}, maximum observed plasma concentration
C_{tr}, trough plasma concentration
CABP, community-acquired bacterial pneumonia
CART, classification and regression tree analysis
CE, clinically evaluable analysis population
CI, confidence interval
CL, plasma clearance
CL_{Non-R}, non-renal clearance
CL_R, renal clearance
CLSI, Clinical and Laboratory Standards Institute
CrCL, creatinine clearance
CRO, ceftriaxone
cSSSI, complicated skin and skin structure infections
CV, coefficient of variation
CYP450, cytochrome P450
DC-TEAE, discontinuation due to treatment-emergent adverse event
ESBL, extended-spectrum β-lactamase
ESRD, end-stage renal disease
f, free unbound (i.e., microbiologically active) drug
*f*T>MIC, time of free drug concentrations above the minimum inhibitory concentration
HD, hemodialysis
HPLC, high performance liquid chromatography
IM, intramuscular
IRT, Interdisciplinary Review Team for QT Studies
IV, intravenous
LC-MS/MS, liquid chromatography with tandem mass spectrometry
LLOQ, lower limit of quantification
MIC, minimum inhibitory concentration
MIC_{50}, minimum inhibitory concentration for 50% of bacterial population
MIC_{90}, minimum inhibitory concentration for 90% of bacterial population
MITT, modified intent-to-treat analysis population
MITTE, modified intent-to-treat efficacy analysis population
MRSA, methicillin-resistant *Staphylococcus aureus*
MSSA, methicillin-susceptible *Staphylococcus aureus*
NDA, new drug application
P-gp, P-glycoprotein
PAE, post-antibiotic effect
PBP, penicillin-binding protein
PD, pharmacodynamics

PISP, penicillin-intermediate *Streptococcus pneumoniae*
PK, pharmacokinetics
PK-PD, pharmacokinetics-pharmacodynamics
PRSP, penicillin-resistant *Streptococcus pneumoniae*
PSSP, penicillin-susceptible *Streptococcus pneumoniae*
Q12h, every 12 hours
Q24h, every 24 hours
QC, quality control
QTcIb, QT interval corrected for heart rate using individual subject correction formula based on baseline QT-RR slope
ΔQTcIb, change in QTcIb from baseline
ΔΔQTcIb, between-treatment difference in ΔQTcIb
SAE, serious adverse event
SD, standard deviation
$t_{1/2}$, elimination half-life
T_{max}, time of maximum observed plasma concentration
TEAE, treatment-emergent adverse event
TOC, test-of-cure visit
ULOQ, upper limit of quantification
V_c, apparent volume of distribution of the central compartment
V_p, apparent volume of distribution of the peripheral compartment
V_{ss}, apparent steady-state volume of distribution
V_z, apparent volume of distribution of the terminal phase
VAN, vancomycin

1. EXECUTIVE SUMMARY

Cerexa Inc., submitted a New Drug Application (NDA) for ceftaroline fosamil for the treatment of complicated skin and skin structure infections (cSSSI) and community-acquired bacterial pneumonia (CABP) caused by susceptible organisms. Ceftaroline fosamil is a semi-synthetic cephalosporin prodrug that is converted *in vivo* to the microbiologically active ceftaroline. The proposed clinical dosing regimen for ceftaroline fosamil is 600 mg every 12 hours (Q12h) by intravenous (IV) infusion over 1 hour in adults ≥18 years of age for 5-14 days for treatment of cSSSI and for 5-7 days for treatment of CABP.

Clinical components of the ceftaroline fosamil NDA are summarized as follows:

- Seven *in vitro* studies with human biomaterials were submitted, evaluating plasma protein binding, biotransformation of prodrug in plasma, metabolism in hepatic microsomes, and inhibition/induction of cytochrome P450 (CYP450) isoenzymes.
- Eleven Phase 1 studies evaluating pharmacokinetics of ceftaroline fosamil and relevant metabolites, including the bioactive ceftaroline, were submitted. Studies included single- and multiple-dose pharmacokinetics; metabolism and elimination via mass balance and metabolite profiling; effect of renal impairment (mild, moderate, severe, and end-stage renal disease [ESRD] on intermittent hemodialysis [HD]), age (elderly and adolescent), and gender; and impact on intestinal microflora and QT prolongation. All Phase 1 studies were conducted with IV infusions of ceftaroline fosamil except for one which utilized intramuscular [IM] administration.
- Two supportive Phase 2 trials evaluating safety/efficacy of ceftaroline fosamil versus active comparators in the treatment of cSSSI were submitted. In P903-03, ceftaroline fosamil 600 mg Q12h as a 1-hour IV infusion was compared to vancomycin with optional aztreonam. In P903-19, ceftaroline fosamil 600 mg Q12h as IM injection was compared to linezolid with optional aztreonam.
- Four pivotal Phase 3 trials evaluating safety/efficacy of ceftaroline fosamil versus active comparators in the treatment of cSSSI and CABP were submitted. For cSSSI, ceftaroline fosamil 600 mg Q12h as a 1-hour IV infusion was compared to vancomycin 1 g IV Q12h + aztreonam 1 g IV Q12h for 5-14 days in two Phase 3 trials (P903-06 and P903-07). For CABP, ceftaroline fosamil 600 mg Q12h as a 1-hour IV infusion was compared to ceftriaxone 1 g IV Q24h for 5-7 days in two Phase 3 trials (P903-08 and P903-09).

1.1 Recommendations

The Office of Clinical Pharmacology, Division 4 has reviewed NDA 200-327, and it is acceptable from a clinical pharmacology perspective. The Reviewer's recommendations for dose adjustment for renal impairment should be incorporated in the label as indicated in **Table 1.1-1**.

Table 1.1-1 Dose recommendations for ceftaroline fosamil by renal function

Renal Function	Creatinine Clearance (mL/min)	Recommended Ceftaroline Fosamil Regimens[a]	
		By Sponsor	By Reviewer
Normal renal function	>80	(b) (4)	600 mg Q12h
Mild renal impairment	>50 to ≤80		600 mg Q12h
Moderate renal impairment	>30 to ≤50		***400 mg Q12h***
Severe renal impairment	≤30		***300 mg Q12h***
End-stage renal disease (ESRD)	(On hemodialysis [HD])		***200 mg Q12h, dose post-HD on HD days***

[a] All doses are as 1-h IV infusions

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Exposure-Response

Efficacy: Characteristic of β-lactams, %*f*T>MIC (i.e., percentage of the dosing interval that free drug concentrations are greater than the MIC) for ceftaroline was best associated with *in vivo* efficacy in a neutropenic murine thigh model against *S. aureus* (n=4, methicillin-susceptible [MSSA] and -resistant [MRSA]) and *S. pneumoniae* (n=5). Median %*f*T>MIC ≥51 was associated with 2-log kill (99% reduction) against *S. aureus* and *S. pneumoniae* strains, in accordance with historical PK-PD data of cephalosporins (optimal %*f*T>MIC, 50-70). Median %*f*T>MIC associated with bacteriostasis against *S. aureus* and *S. pneumoniae* isolates were ≥26 and ≥35, respectively.

Exposure-response analysis with population PK models indicated a significant positive relationship (p=0.027) between %*f*T>MIC and per-patient microbiological response in microbiologically evaluable (ME) patients with mono- or poly-microbial *S. aureus* or *S. pyogenes* cSSSI (n=449). Unlike for cSSSI, an exposure-response relationship was not identified for CABP, as majority of Phase 3 patients had a high and limited range of ceftaroline exposures (91.7-100%*f*T>MIC).

Based on PK-PD target attainment analyses by Monte Carlo simulation, ceftaroline exposures associated with bacteriostasis were predicted to be achieved at MIC ≤2 µg/mL against *S. aureus* and at MIC ≤1 µg/mL against *S. pneumoniae* for the proposed clinical regimen of ceftaroline fosamil 600 mg Q12h.

Safety: Most common treatment-emergent adverse events (TEAE) with ceftaroline in Phase 1 studies and Phase 3 trials were gastrointestinal disorders (nausea, vomiting, diarrhea, and constipation) and headache. In pooled Phase 1 studies where healthy adults were administered single IV doses of 50-2000 mg and multiple IV doses of 600-1800 mg/day, the percentage of subjects who experienced any TEAE was slightly greater (by 6.5%) with ceftaroline (n=236) versus placebo (n=78). In pooled Phase 3 trials, percentages of subjects with TEAE, serious adverse event (SAE), or discontinuation due to TEAE with ceftaroline (n=1305) were similar to or lower than that of comparator agents for cSSSI and CABP (n=1301).

Ceftaroline had minimal effect on intestinal microflora (as change in median bacterial counts or new colonizing organisms with increased ceftaroline MIC) in a Phase 1 study of healthy adults (n=12) following multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12h for 7 days (P903-14). However, the possibility of *Clostridium difficile*-associated diarrhea (known risk for nearly all antibacterial agents) cannot be excluded.

No significant QT prolongation was detected at the supratherapeutic dose of ceftaroline fosamil (1500 mg as single 1-hour IV infusion) in a thorough QT study of 54 healthy adults (P903-05). The largest upper bound of the two-sided 90% confidence interval for mean difference between ceftaroline fosamil 1500 mg and placebo was below the threshold for regulatory concern (10 msec).

1.3.2 Pharmacokinetics

General Pharmacokinetics: Ceftaroline fosamil (prodrug) is rapidly converted during IV infusion by *in vivo* phosphatase enzymes to the active ceftaroline. Ceftaroline is the predominant circulating compound in plasma, and exhibits linear pharmacokinetics with approximately dose-proportional increase in exposure over the studied single dose range of 50-1000 mg (P903-01). The β-lactam ring of ceftaroline undergoes hydrolysis to form the inactive, open-ring metabolite, ceftaroline M-1.

Pharmacokinetic parameters of ceftaroline and ceftaroline M-1 following single and multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12h in healthy adults are summarized in **Table 1.3.2-1** (P903-01). Due to rapid biotransformation, concentrations of ceftaroline fosamil were generally measurable only during IV infusion.

Table 1.3.2-1 Mean ± SD pharmacokinetic parameters following single and multiple 1-h IV infusions of ceftaroline fosamil in healthy adults

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

Distribution: Plasma protein binding of ceftaroline is approximately 20% in humans and decreases minimally with increasing concentration over clinically relevant concentrations (1-50 µg/mL, 14.5-28.0% bound).

Metabolism: The cytochrome P450 (CYP450) enzymatic system does not appear to be a significant metabolic pathway for ceftaroline, as low metabolic turnover (<12%) was observed in an *in vitro* study of pooled human liver microsomes.

Ceftaroline fosamil, ceftaroline, ceftaroline M-1, and three minor unidentified metabolites were detected in plasma following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg in healthy young adult males (n=6) (P903-13). Ceftaroline was the predominant compound systemically available, followed by ceftaroline M-1, which was approximately 20% of the area under the concentration-time curve from time 0 to infinity (AUC_{inf}) for ceftaroline.

Excretion: Ceftaroline and accompanying metabolites are primarily eliminated through renal excretion. Approximately 64.3% of the dose was recovered in urine as unchanged ceftaroline and 2.3% as ceftaroline M-1 in healthy young adult males (n=6) following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg (P903-13).

1.3.3 Intrinsic Factors

Elderly: Pharmacokinetics of ceftaroline were evaluated in healthy elderly (≥65 years of age) subjects versus healthy young adult (18-45 years of age) subjects with equal number of males and females, following single 1-hour IV infusion of ceftaroline fosamil 600 mg (P903-11). Mean plasma clearance (CL) of ceftaroline was 25% lower in elderly subjects (n=16) than in young adults (n=16), and accordingly, ceftaroline AUC_{inf} for ceftaroline was 33% greater in the elderly cohort based on geometric mean ratio. Modestly higher exposures in elderly subjects could be attributed to decreased renal function, as median creatinine clearance (CrCL) was 79.3 (61.2-106.9) mL/min for those ≥65 years of age versus 125.3 (106.1-159.4) mL/min for those 18-45 years of age.

No dose adjustment is necessary based on age.

Pediatric (Adolescent): Pharmacokinetics of ceftaroline were evaluated in hospitalized adolescent (12-17 years of age) subjects receiving antibiotic therapy, following single 1-hour IV infusion of ceftaroline fosamil 8 mg/kg for those <75 kg or 600 mg for those ≥75 kg (P903-15). Mean estimates of CL and volume of distribution of the terminal phase (V_z) for ceftaroline were similar between adolescent subjects (n=7) in this study and healthy adults (n=6) administered single 600 mg doses in a separate Phase 1 study (P903-01). Based on single-dose pharmacokinetic data, it appears the fixed adult dose of 600 mg would be appropriate for adolescent patients.

The Sponsor has requested deferral of pediatric assessment as a Phase 4 commitment for both cSSSI and CABP indications of the following age groups: adolescents (≥12 years to <18 years), children (≥24 months to <12 years), infants/toddlers (≥28 days to <24 months), and neonates (0 days to <28 days).

Gender: Pharmacokinetics of ceftaroline were evaluated in healthy elderly males and females and healthy young adult males and females following single 1-hour IV infusion of ceftaroline fosamil 600 mg (P903-11). There was a trend for slightly higher C_{max} (17%) and AUC_{inf} (6-15%) in females across age/gender cohorts of elderly males (n=10) versus elderly females (n=6) and young adult males (n=6) versus young adult females (n=10). Modest differences in ceftaroline exposures could be partly attributed to lower body weight in females.

No dose adjustment based on gender is necessary.

Renal impairment: Pharmacokinetics of ceftaroline were evaluated in subjects with mild (CrCL >50 to ≤80 mL/min) and moderate (CrCL >30 to ≤50 mL/min) renal impairment (P903-02), severe (CrCL ≤30 mL/min) renal impairment (P903-04), and ESRD subjects dosed pre- and post-HD (P903-18) versus subjects with normal renal function (CrCL >80 mL/min) in three separate Phase 1 studies (**Table 1.3.3-1**). CrCL, when estimated, was determined by Cockcroft-Gault calculations.

Table 1.3.3-1 Mean pharmacokinetic parameters for ceftaroline following single 1-h IV infusion of ceftaroline fosamil in subjects with mild, moderate, or severe renal impairment, and ESRD subjects on HD versus subjects with normal renal function

Parameter	P903-02			P903-04		P903-18	
	Normal 600 mg (n=6)	**Mild 600 mg (n=6)**	**Moderate 600 mg (n=6)**	**Normal 400 mg (n=6)**	**Severe 400 mg (n=6)**	**Normal 400 mg (n=6)**	**ESRD 400 mg, Post-HD (n=6)**
CrCL (mL/min)[a]	109.2 (91.7-133.8)	60.2 (51.8-71.0)	35.0 (30.1-42.5)	99.5 (80.2-139.0)	23.0 (15.0-30.0)	119.3 (101.4-168.9)	–
Ceftaroline							
C_{max} (µg/mL)	28.35	28.17	30.83	14.75	17.87	16.48	29.10
AUC_{inf} (µg*h/mL)	75.56	92.27	114.84	52.81	113.32	48.63	128.58
$t_{1/2}$ (h)	2.87	3.67	4.60	3.02	5.05	2.75	6.16
CL (L/h)	7.11	6.12	4.68	6.90	3.22	7.47	2.77
CL_R (L/h)	3.36	1.87	1.20	4.38	0.71	4.55	–
V_z (L)	29.27	32.87	30.48	29.53	22.77	29.59	24.58
V_{ss} (L)	–	–	–	22.91	20.74	21.30	20.69
Ae (%)	46.77	32.19	25.83	62.32	22.88	60.40	–

[a] CrCL expressed as median (minimum-maximum)

Ceftaroline CL, renal clearance (CL_R), and amount of drug excreted in urine (Ae) decreased with declining renal function (as CrCL) across studies, while V_z and steady-state volume of distribution (V_{ss}) appeared unaffected by renal impairment. Accordingly, mean elimination half-life ($t_{1/2}$) for ceftaroline was extended from ~3 hours with normal renal function to ~6 hours with ESRD (longest $t_{1/2}$ of renally-impaired cohorts). When doses were administered pre-HD in ESRD subjects, approximately 21.6% of the dose was removed by the dialysis procedure.

Dose adjustments are recommended for patients with moderate and severe renal impairment and for ESRD patients on intermittent HD as indicated in **Table 1.3.3-2**. Renal-adjusted dosing regimens were derived using data from Phase 1 renal impairment studies to match steady-state exposures of the active compound, ceftaroline, by AUC_{tau} and % *f*T>MIC to that of subjects with normal renal function receiving the proposed clinical regimen of ceftaroline fosamil 600 mg Q12h as a 1-hour IV infusion.

Table 1.3.3-2 Median ceftaroline exposure (observed and simulated) for recommended dosing regimens of ceftaroline fosamil by the Reviewer (in bold and italicized font) according to renal function

Renal Function	CrCL (mL/min)	Dosing Regimen[a]	Ceftaroline AUC_{tau} (µg*h/mL)		
			Observed		Simulated
			Phase 1 -02, -04, -18	Phase 2/3 -03, -06, -07, -08, -09	Phase 1 -02, -04, -18
			Non-Compartmental	Population PK	Two-Compartmental (Reviewer)
Normal	>80	***600 mg Q12h***	74.9[b] (n=6)	54.9 (n=140)	72.1 (n=17)
Mild	>50 to ≤80	***600 mg Q12h***	92.7[b] (n=6)	75.0 (n=62)	–
Moderate	>30 to ≤50	***400 mg Q12h***	–	69.6 (n=17)	75.3 (n=6)
Severe	≤30	400 mg Q12h	113.6[b] (n=6)	–	107.9 (n=6)
		300 mg Q12h	–	–	81.0 (n=6)
ESRD	(on HD)	***200 mg Q12h***	–	–	64.9 (n=6)

[a] All simulated doses were as 1-h IV infusions
[b] Phase 1 subjects received single doses of ceftaroline fosamil; values represent AUC_{inf} rather than AUC_{tau}

1.3.4 Extrinsic Factors

Drug-drug interactions: *In vitro* studies indicate ceftaroline is not an inhibitor or inducer of major CYP450 isoenzymes, and thus, *in vivo* drug interactions with known CYP450 substrates are unlikely. In an exploratory population PK analysis of Phase 2/3 patients with cSSSI or CABP, no clinically significant differences in ceftaroline C_{max} or AUC_{tau} were observed with concomitant medication use including substrates, inhibitors, or inducers of major CYP450 isoenzymes; anionic or cationic drugs known to undergo active renal secretion; and vasodilator or vasoconstrictor drugs that may alter renal blood flow.

2. QUESTION-BASED REVIEW

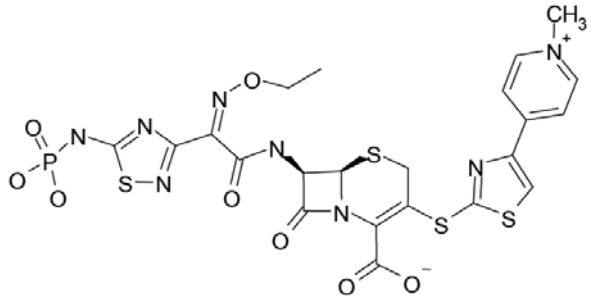
2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

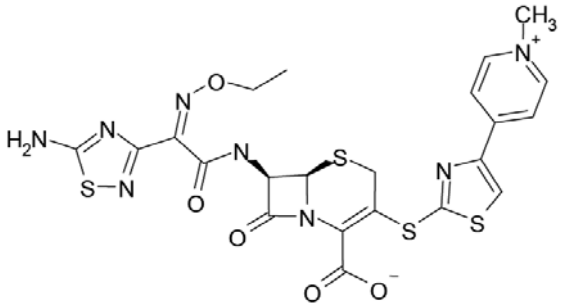
Ceftaroline fosamil (previously TAK-599 and PPI-0903) is a semi-synthetic cephalosporin prodrug that is rapidly converted *in vivo* to the microbiologically active ceftaroline (previously M-1, T-91825, and PPI-0903M). Ceftaroline displays broad *in vitro* activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria frequently implicated in skin and respiratory infections.

The chemical name of ceftaroline fosamil is (6R,7R)-7-{(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. The molecular formula of ceftaroline fosamil is $C_{22}H_{21}N_8O_8PS_4$ and the molecular weight is 684.68 g/mol. The molecular weight of ceftaroline is 604.70 g/mol. The prodrug form of ceftaroline contains an N-phosphono group that confers enhanced solubility in water; structures of ceftaroline fosamil (prodrug) and ceftaroline (active) are pictured below.

Ceftaroline fosamil (prodrug)



Ceftaroline (active)



Ceftaroline Fosamil for Injection contains a sterile (b) (4) ceftaroline fosamil drug substance (acetic acid solvate monohydrate) and L-arginine, (b) (4), in a (b) (4) mass ratio. The finished drug product is packaged in single-dose units of 600 mg/vial

and 400 mg/vial containing 600 mg and 400 mg of ceftaroline fosamil (anhydrous [redacted]), respectively, in clear, 20-cc, Type I glass vials with [redacted] rubber injection stoppers and aluminum/lacquered flip cap overseals. Contents of the vial are reconstituted with 20 mL of Sterile Water for Injection USP, and then further diluted in ≥250 mL of an appropriate infusion solution. Reconstituted solution in the infusion bag should be used within 6 hours when stored at room temperature or within 24 hours when stored under refrigeration at 2-8 ºC.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indications(s)?

Ceftaroline belongs to the cephalosporin class of antibiotics and shares the bactericidal mechanism of action of other β-lactams. Ceftaroline inhibits cell wall biosynthesis, mediated through binding to essential penicillin-binding proteins (PBP). Unlike most β-lactams, ceftaroline is active against methicillin-resistant *Staphylococcus aureus* (MRSA) due to high affinity for PBP2a and against *Streptococcus pneumoniae* with reduced susceptibility to penicillin due to high affinity for PBP2x.

The proposed indications for ceftaroline fosamil are treatment of complicated skin and skin structure infections (cSSSI) and community-acquired bacterial pneumonia (CABP) caused by designated susceptible bacteria as indicated below:

cSSSI

- *Staphylococcus aureus* (methicillin-susceptible [MSSA] and -resistant isolates)
- *Streptococcus pyogenes, Streptococcus agalactiae,* [redacted]
- [redacted]
- *Escherichia coli*
- *Klebsiella pneumoniae, Klebsiella oxytoca*
- [redacted]

CABP

- *Streptococcus pneumoniae* [redacted]
- *Staphylococcus aureus*
- *Haemophilus influenzae,* [redacted]
- *Klebsiella pneumoniae*
- *Escherichia coli*

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Ceftaroline fosamil is intended for intravenous (IV) administration. The proposed clinical dose of ceftaroline fosamil is 600 mg every 12 hours (Q12h) by IV infusion administered over 1 hour in adults ≥18 years of age for 5-14 days for treatment of cSSSI and 5-7 days for treatment of CABP. Dose adjustments are recommended for patients with renal impairment (see **Section 2.3.2.5** for details).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In total, there were seven *in vitro* studies and eleven Phase 1 studies (nine reviewed) evaluating the clinical pharmacology of ceftaroline fosamil and relevant metabolites, including the active ceftaroline. Studies included single- and multiple-dose pharmacokinetics; metabolism and elimination via mass balance and metabolite profiling; effect of renal impairment (mild, moderate, severe, and end-stage renal disease [ESRD] on intermittent hemodialysis [HD]), age (elderly and adolescent), and gender; and impact on intestinal microflora and QT prolongation. Data from Phase 1 studies were also used along with pharmacokinetic data obtained from two Phase 2 trials and four Phase 3 trials for development of population pharmacokinetic (PK) models.

All clinical studies were conducted with IV infusions of ceftaroline fosamil except for two (one Phase 1 study and one Phase 2 cSSSI trial), which utilized the intramuscular (IM) route of administration. (b) (4)

Efficacy of ceftaroline fosamil in the treatment of cSSSI was assessed in two pivotal Phase 3 IV trials (**P903-06** and **P903-07**) and two supportive Phase 2 trials (**P903-03** with IV and **P903-19** with IM) as summarized in **Table 2.2.1-1**. In the treatment of CABP, efficacy was assessed in two pivotal Phase 3 IV trials (**P903-08** and **P903-09**) as summarized in **Table 2.2.1-2**. All ceftaroline-treated patients in Phase 2/3 trials received the proposed regimen of 600 mg Q12h (adjusted to 400 mg Q12h for those with moderate renal impairment, defined as creatinine clearance [CrCL] >30 to ≤50 mL/min).

Table 2.2.1-1 Overview of clinical efficacy trials for ceftaroline fosamil in the treatment of **cSSSI**

Study No.	Design	Ceftaroline Fosamil Regimen	Comparator Regimen	Treatment Duration	Population Size
Phase 3					
P903-06	Multicenter, randomized, double-blind, comparative study	600 mg Q12h (1-h IV infusion) [400 mg Q12h for CrCL >30 to ≤50 mL/min]	Vancomycin 1 g IV Q12h + Aztreonam 1 g IV Q12h	5-14 days	Ceftaroline N = 353 Comparator N = 349
P903-07					Ceftaroline N = 348 Comparator N = 346
Phase 2					
P903-03	Multicenter, randomized, observer-blind, active-control study	600 mg Q12h (1-h IV infusion)	Vancomycin 1 g IV Q12h (+ optional Aztreonam 1 g IV Q8h)	7-14 days	Ceftaroline N = 67 Comparator N = 33
P903-19	Multicenter, randomized, open-label, active-control study	600 mg Q12h (*IM injection) [400 mg Q12h for CrCL >30 to ≤50 mL/min]	Linezolid 600 mg IV Q12h (+ optional Aztreonam 1 g IV Q12h)	5-14 days	Ceftaroline N = 103 Comparator N = 47

Note: Adapted from Module 5.3.5., Integrated Summary of Clinical Efficacy – cSSSI, Table 6.1-1

Table 2.2.1-2 Overview of clinical efficacy trials for ceftaroline fosamil in the treatment of **CABP**

Study No.	Design	Ceftaroline Fosamil Regimen	Comparator Regimen	Treatment Duration	Population Size
Phase 3					
P903-08	Multicenter, randomized, double-blind, comparative study	600 mg Q12h (1-h IV infusion) + Clarithromycin 500 mg PO ×2 [400 mg Q12h for CrCL >30 to ≤50 mL/min]	Ceftriaxone 1 g IV Q24h + Clarithromycin 500 mg PO ×2	5-7 days	Ceftaroline N = 305 Comparator N = 309
P903-09		600 mg Q12h (1-h IV infusion) [400 mg Q12h for CrCL >30 to ≤50 mL/min]	Ceftriaxone 1 g IV Q24h		Ceftaroline N = 317 Comparator N = 310

Note: Adapted from Module 5.3.5, Integrated Summary of Clinical Efficacy – CABP, Table 6.1-1

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

For cSSSI, the primary efficacy endpoint defined by the Sponsor in Phase 3 studies (**P903-06** and **P903-07**) was clinical response (cure, failure, or indeterminate) at Test-of-Cure (TOC; 8-15 days after End-of-Therapy) in the co-primary Modified Intent-to-Treat (MITT) and Clinically Evaluable (CE) populations (**Table 2.2.2-1**). MITT population was defined as all randomized subjects who received any amount of study drug, and CE population was defined as all MITT subjects who met minimal disease criteria for cSSSI and for whom sufficient information regarding the cSSSI was available to determine the subject's outcome.

For CABP, the primary efficacy endpoint defined by the Sponsor in Phase 3 studies (**P903-08** and **P903-09**) was clinical response (cure, failure, or indeterminate) at TOC in the co-primary Modified Intent-to-Treat Efficacy (MITTE) and CE populations (**Table 2.2.2-1**). MITTE population was defined as all MITT subjects who were PORT (scoring system for risk of mortality in CABP) Risk Class III or IV, and CE population was defined as all MITTE subjects who met minimal disease criteria for CABP and for whom sufficient information regarding the CABP was available to determine the subject's outcome.

Table 2.2.2-1 Efficacy of ceftaroline in pooled Phase 3 trials for cSSSI and CABP **(by Sponsor)**

Clinical Cure	Ceftaroline	Comparator	Weighted Difference (95% Confidence Interval)
Phase 3 cSSSI (-06, -07)			
MITT	595/693 (85.9%)	586/685 (85.5%)	0.3 (-3.4, 4.0)
CE	559/610 (91.6%)	549/592 (92.7%)	-1.1 (-4.2, 2.0)
Phase 3 CABP (-08, -09)			
MITTE	479/580 (82.6%)	439/573 (76.6%)	6.0 (1.4, 10.7)
CE	387/459 (84.3%)	349/449 (77.7%)	6.6 (1.6, 11.8)

Note1: Adapted from Module 5.3.5., Integrated Summary of Clinical Efficacy – cSSSI, Table 3.2.1-1
Note2: Adapted from Module 5.3.5, Integrated Summary of Clinical Efficacy – CABP, Table 3.2.2-1

Analysis populations and endpoints for cSSSI and CABP were based on working draft FDA Guidance documents and/or past meetings between the Sponsor and the Division. It should be emphasized that selected analysis populations and endpoints were defined by the Sponsor and do

not necessarily reflect the Division's current scientific position. Refer to reviews by Statistical Reviewers and Medical Officers for complete analysis of ceftaroline efficacy in cSSSI (C Kadoorie, PhD and N Rellosa, MD) and CABP (D Rubin, PhD and A Porcalla, MD).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Bioanalytical methods were developed and validated to support the quantification of ceftaroline fosamil (prodrug), ceftaroline (active), and ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline) in samples generated from clinical studies. Details regarding validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assays for quantification of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma, urine, and dialysate fluid were reported and acceptable. Additionally, a non-validated radiometric high-performance liquid chromatography (HPLC) assay was used for semi-quantitative purposes of metabolite profiling in plasma, urine, and feces in the mass balance study (**P903-13**). (See **Section 2.6** for details.)

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

***In Vitro* Susceptibility:** Ceftaroline susceptibility (as minimum inhibitory concentration [MIC]) against clinical US isolates of Gram-positive and Gram-negative bacteria from a 2008 surveillance study (**P0903-M-035**) are shown in **Table 2.2.4.1-1**. Ceftaroline displays potent *in vitro* activity against *S. aureus* and *S. pneumoniae*, the predominant causative pathogens of cSSSI and CABP, respectively. Activity against resistant phenotypes such as MRSA, penicillin-non-susceptible *S. pneumoniae*, and β-lactamase producing *H. influenzae* were generally retained as MIC_{90} values increased by only 1-2 dilutions. Ceftaroline was active against wild-type strains of Enterobacteriaceae, but limited against extended-spectrum β-lactamase (ESBL) producers or AmpC β-lactamase hyperproducers (data not shown). Limited activity was also observed against non-fermenting Gram-negative bacilli such as *P. aeruginosa*.

Table 2.2.4.1-1 Ceftaroline activity against key organisms collected in Jan-Dec 2008 from 27 US sites

Organism	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
S. aureus	3965	0.5	1
Methicillin-susceptible	1711	0.25	0.25
Methicillin-resistant	2254	1	1
Coagulase-negative staphylococci	638	0.25	0.5
S. pneumoniae	894	0.015	0.12
Penicillin-susceptible (MIC ≤2)	773	≤0.008	0.12
Penicillin-non-susceptible (MIC ≥4)	121	0.25	0.25
Enterococcus spp.	1202	4	>16
Viridans group streptococci	110	0.03	0.12
β-hemolytic streptococci	327	≤0.008	0.03
E. coli	1076	0.12	0.5
Klebsiella spp.	706	0.12	>16
Enterobacter spp.	403	0.25	>16
Citrobacter spp.	79	0.25	>16
P. mirabilis	120	0.12	0.25
Serratia spp.	182	1	4
H. influenzae	381	≤0.008	0.015
B-lactamase negative	275	≤0.008	0.015
B-lactamase positive	106	≤0.008	0.03

Note: Adapted from Module 5.3.5, Study P0903-M-035, Table 3

Time-Kill Kinetics: Ceftaroline showed bactericidal effects (i.e., ≥3-log kill) within 8-24 hours against *S. aureus* (n=6, MSSA and MRSA), *S. pneumoniae* (n=4, isolates with varying penicillin susceptibility), wild-type Enterobacteriaceae (n=4), and *H. influenzae* (n=1) (**P0903-M-001, Part II**). Bacterial killing did not improve with increasing concentration (2, 4, or 8 times the MIC) and was generally maximized at 2 times the MIC as expected for non-concentration-dependent β-lactam agents.

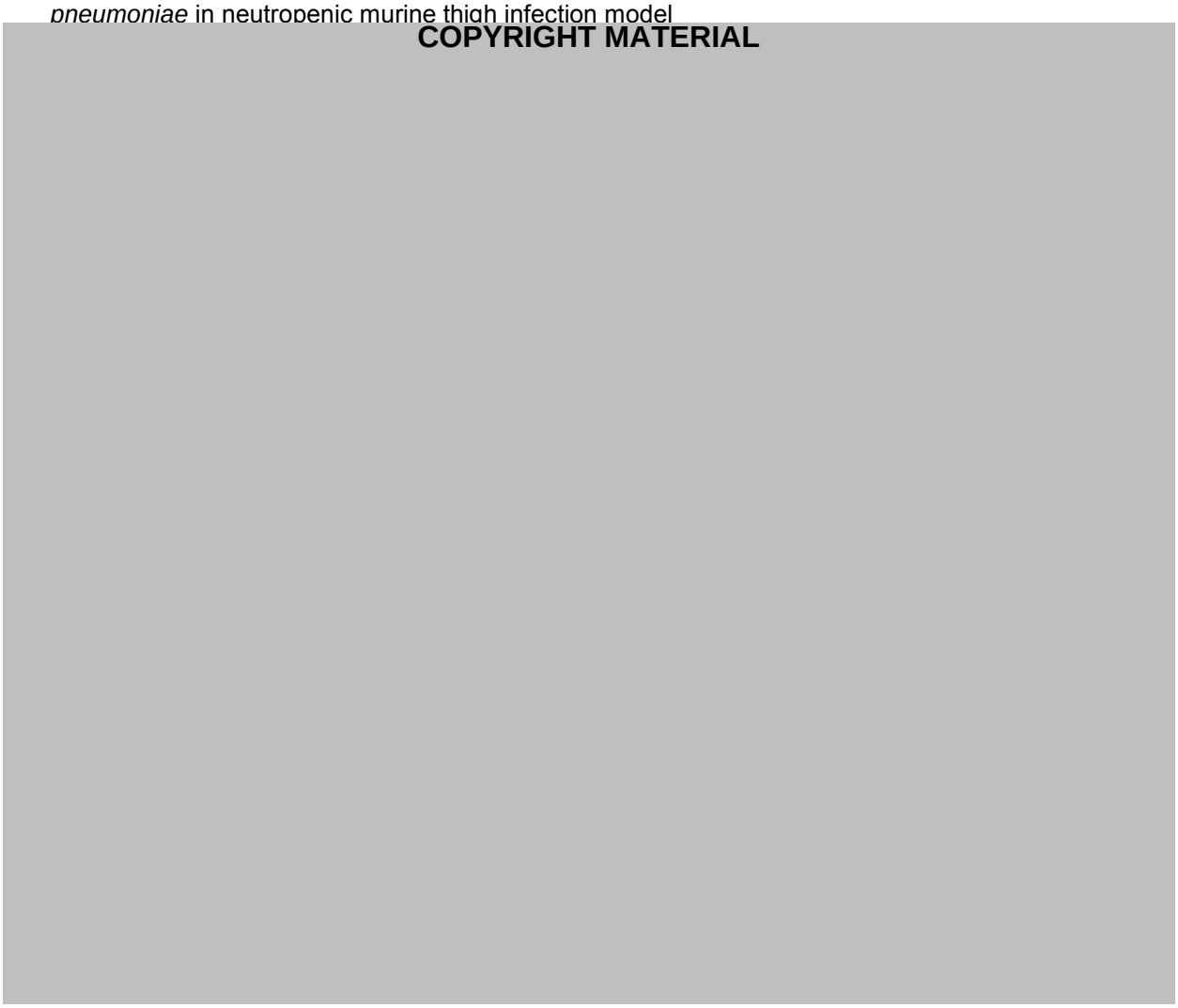
Post-Antibiotic Effect: Most β-lactams are known to exhibit short to moderate post-antibiotic effect (PAE) against Gram-positive organisms while negligible against Gram-negative organisms (except for carbapenems against *P. aeruginosa*). Fittingly, ceftaroline displayed short PAEs against *S. aureus* and *S. pneumoniae* of various resistance phenotypes following 1-hour treatment with concentrations 10 times the MIC and 1000-fold dilution into fresh broth media in studies **P0903-M-055** (*S. aureus*, 0.8-1.4 h; *S. pneumoniae*, 1.4-2.2 h) and **P0903-M-056** (*S. aureus*, 0.7-2.2 h; *S. pneumoniae*, 0.7-1.8 h), respectively. Ceftaroline PAEs against *E. coli*, *K. pneumoniae* and *H. influenzae* isolates were generally not observed.

Ceftaroline PAE was also assessed *in vivo* against *S. aureus* (n=1, MSSA) and *S. pneumoniae* (n=1, penicillin-susceptible [PSSP]) in a neutropenic murine thigh infection model, following single subcutaneous doses of 1.56, 6.25, 25, and 100 mg/kg with respective C_{max} of 3.44, 6.25, 9.89, and 100 µg/mL (**P0903-M-003**; **Andes D and Craig WA**. *Antimicrob Agents Chemother* 2006;50:1376-1383.). Free drug concentrations of ceftaroline were estimated to be above the MIC for 0.17, 0.84, 4.2, and 4.6 h, respectively, for *S. aureus* (MIC 0.25 µg/mL), and for 4.3, 5.9, 8.0, and 8.2 h, respectively, for *S. pneumoniae* (MIC 0.008 µg/mL). Depending on dose, PAEs ranged 0.8 to 7.2 h for *S. aureus* and -1.9 to 1.5 h for *S. pneumoniae*. (Note: *In vivo* PAE was also investigated against *E. coli*, however, reported results were discordant between P0903-M-003 Study Report and published literature. It is unclear as to which results are correct, and as such, these results were disregarded.)

Animal Infection Models: *In vivo* efficacy of ceftaroline has been evaluated in various animal infection models, of which the pharmacokinetic-pharmacodynamic (PK-PD) relationship was characterized in neutropenic and non-neutropenic murine thigh and lung models (**P0903-M-003**; **Andes D and Craig WA**. *Antimicrob Agents Chemother* 2006;50:1376-1383.). Various isolates of *S. aureus* (n=4, MSSA and MRSA), *S. pneumoniae* (n=5), and Enterobacteriaceae (n=4, *E. coli* and *K. pneumoniae*) were tested in neutropenic thigh-infected mice with a dose range of 0.40-1600 mg/kg/day in divided Q6h doses. Free (i.e., microbiologically active, *f*) drug exposures were determined in serum by evaluating single-dose pharmacokinetics of 1.56-100 mg/kg via bioassay and correcting for murine protein binding (63-66%).

Characteristic of β-lactams, the amount of time (expressed as % of the dosing interval) that free drug concentrations are greater than the MIC (*f*T>MIC) was identified as the pharmacodynamic parameter best predictive of ceftaroline efficacy (as change in bacterial density) following dose fractionation studies (0.39-100 mg/kg/day in divided 1, 2, 4, or 8 doses) (**Figure 2.2.4.1-1**).

Figure 2.2.4.1-1 Relationships of ceftaroline PK-PD indices to *in vivo* efficacy against *S. aureus* and *S. pneumoniae* in neutropenic murine thigh infection model



Note: Adapted from Andes D and Craig WA. Antimicrob Agents Chemother 2006;50:1376-1383.

Approximately 50% *f*T>MIC was correlated with 2-log kill against *S. aureus* and *S. pneumoniae* strains, in accordance with historical PK-PD data of cephalosporins (optimal *f*T>MIC, 50-70%) (**Table 2.2.4.1-2**). Results against Enterobacteriaceae, however, were considerably discordant between P0903-M-003 Study Report (mean *f*T>MIC for 2-log kill, 88%) and published literature (mean *f*T>MIC for 2-log kill, 54%), and as such, were disregarded in light of uncertainty of data. (Note: Reported penicillin susceptibility of tested *S. pneumoniae* were based on earlier interpretive criteria by the Clinical Laboratory Standards Institute [CLSI], where susceptible, intermediate [PISP], and resistant [PRSP] breakpoints were ≤0.06, 0.12-1, and ≥2 µg/mL, respectively.)

Table 2.2.4.1-2 *In vivo* efficacy (as change in $\log_{10}$ CFU/thigh) of ceftaroline in neutropenic murine thigh infection model

Based on CLSI suscept bility criteria before 2009, when non-meningitis breakpoint for penicillin changed from ≤0.06 to ≤2 µg/mL
Note: Adapted from Andes D and Craig WA. Antimicrob Agents Chemother 2006;50:1376-1383.

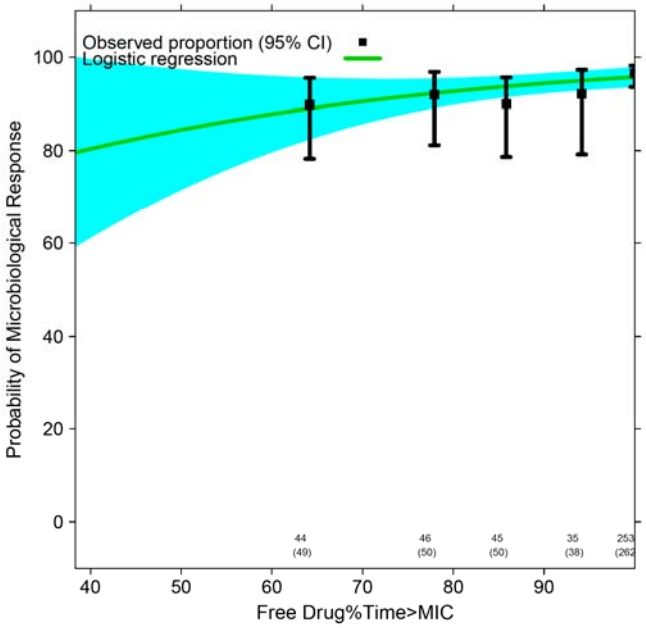
Ceftaroline efficacy was not significantly enhanced by the presence of a functioning immune system and required similar magnitude of exposure for comparable bacterial kill, as was demonstrated with a single *S. pneumoniae* isolate in neutropenic and non-neutropenic thigh-infected mice. Requisite *f*T>MIC for bacteriostasis, 1-log kill, and 2-log kill, respectively, between neutropenic versus non-neutropenic animals were 34% versus 29%, 37% versus 33%, and 43% versus 36%, respectively. (Note: It should be emphasized that data was limited to a single tested isolate.)

Efficacy also did not vary depending on site of infection between neutropenic thigh and lung models tested with a single isolate of *K. pneumoniae*. Although Enterobacteriaceae results in these animal models were discordant between data sources, the magnitude of %*f*T>MIC did not appear to differ from thigh versus lung infections in both P0903-M-003 Study Report and published literature. (Note: It should be emphasized that data was limited to a single tested isolate.)

Population PK-PD: Exposure-response analyses were performed for ceftaroline in ME patients from Phase 2/3 cSSSI and CABP trials with population PK models developed using pharmacokinetic data obtained from Phase 1 studies and Phase 2/3 trials. For cSSSI, logistic

regression analysis of *f*T>MIC versus per-patient microbiological response showed a significant positive relationship (p=0.027) in ME patients with mono- or poly-microbial *S. aureus* or *S. pyogenes* infections (n=449), although 97% of patients had ≥60% *f*T>MIC and overall probability of per-patient microbiological success was >80% (**Figure 2.2.4.1-2**). (Note: Individual estimates from patients with pharmacokinetic data [n=41 from IV dosing; n=42 from IM dosing in P903-19] and population mean predicted concentrations for patients without pharmacokinetic data were used to derive % *f*T>MIC for each evaluable patient.) (Note: Exposure-response analysis by the Pharmacometrics Reviewer was similar to that performed by the Sponsor, whose analysis was limited to mono- or poly-microbial *S. aureus* cSSSI [**ICPD 00174-6**]). (See Pharmacometrics Review under **Section 4, Appendices**.)

Figure 2.2.4.1-2 Relationship between % *f*T>MIC and probability of per-patient microbiological response for ME patients infected with mono- or poly-microbial *S. aureus* or *S. pyogenes* cSSSI (n=449)



Note1: black symbols = observed proportion; solid green line = mean logistic regression prediction; shaded blue area = 95% confidence interval

Other than % *f*T>MIC, age and diabetes were also identified as potential predictors of low per-patient microbiological response in ME patients with mono- or poly-microbial *S. aureus* or *S. pyogenes* cSSSI (n=449) (**Table 2.2.4.1-3**). Other factors such as body weight or body mass index were not found to be significant predictors of low response.

Table 2.2.4.1-3 Proportion test for factors associated with per-patient microbiological response for ME population with mono- or poly-microbial *S. aureus* or *S. pyogenes* cSSSI (n=449)

Per-Patient Microbiological Response Rate		**95% Confidence Interval**	**Chi-Square p-value**
Age >60 years	**Age ≤60 years**		
0.88 (n=78)	0.95 (n=371)	(-0.15, 0.01)	0.03
With diabetes	**Without diabetes**		
0.86 (n=72)	0.96 (n=377)	(-0.187, -0.005)	0.003

An exposure-response relationship was not identified for CABP as the majority of ME patients from Phase 3 trials had a high and limited range of ceftaroline exposures (91.7-100% *f*T>MIC).

PK-PD Target Attainment: An 8000-patient Monte Carlo simulation was performed to assess % *f*T>MIC of simulated patients relative to desired PK-PD target against *S. aureus* (for cSSSI, **ICPD 00174-8**) and against *S. pneumoniae* (for CABP, **ICPD 00174-9**) by MIC for various dosing regimens by renal function category. In brief, parameter estimates and variance-covariance matrix from final population PK models for ceftaroline fosamil and ceftaroline were used to simulate steady-state profiles of ceftaroline for 2000 patients per renal function category as defined by CrCL (mL/min/1.73 m^2): normal renal function (≥80 to ≤170), and mild (≥50 to <80), moderate (≥30 to <50), and severe (<30) renal impairment. Free ceftaroline concentrations were obtained by assuming 20% protein binding; individual predicted concentrations were multiplied by a constant value of 0.8. Patients were assigned a CrCL value based upon uniform distribution for each renal function category except for patients with normal renal function, in which CrCL was assigned according to Gaussian distribution with mean ± standard deviation (SD) of 118 ± 30.8 (based on actual data obtained from Phase 2/3 patients with cSSSI). Within each renal function category, there was an equal distribution of males and females, and within each gender category, age was assigned according to Gaussian distribution with mean ± SD of 46.2 ± 16.6 (based on actual data obtained from Phase 2/3 patients with cSSSI).

Due to discordant results between Monte Carlo simulation and Phase 1 renal impairment studies, only PK-PD target attainment data for normal renal function was deemed applicable (see **Section 2.3.2.5** for details). Median values and corresponding 90% confidence intervals (CI) for steady-state % *f*T>MIC are listed according to MIC in **Table 2.2.4.1-4** for the 600 mg Q12 regimen in 2000 simulated patients with normal renal function.

For *S. aureus*, desired PK-PD targets included ≥26%, ≥36%, and ≥51% *f*T>MIC, median values respectively associated with net bacterial stasis, 1-log kill (90% reduction), and 2-log kill (99% reduction) against *S. aureus* isolates (n=4) in the neutropenic murine thigh model (**Table 2.2.4.1-2**). An additional clinically-derived target for *S. aureus* was ≥55% *f*T>MIC based on exposure-response analysis of Phase 2/3 cSSSI studies by the Sponsor (**ICPD 00174-6**). This PK-PD breakpoint was determined by classification and regression tree (CART) analysis and was associated with higher probabilities of per-patient microbiological success (94.6% [401/424] versus 57.1% [4/7], p=0.006) for patients with mono- or poly-microbial *S. aureus* cSSSI from the ME population (n=431). (Note: The CART-derived breakpoint was interpreted with caution due to the limited number of patients with *f*T>MIC <55% [n=7]).

For *S. pneumoniae*, desired PK-PD targets were ≥35%, ≥44%, and ≥51% *f*T>MIC, median values respectively associated with net bacterial stasis, 1-log kill (90% reduction), and 2-log kill (99% reduction) against pneumococci (n=5) in the neutropenic murine thigh model (**Table 2.2.4.1-2**). (Note: Unlike for cSSSI, an exposure-response relationship could not be determined with Phase 3 CABP studies [**ICPD 00174-7**] since majority of patients had high ceftaroline exposures of 91.7-100% *f*T>MIC.)

Lower bounds of the 90% CI for simulated % *f*T>MIC exceed non-clinical PK-PD targets associated with maximal efficacy (i.e., 2-log kill) for both *S. aureus* and *S. pneumoniae* and the

clinical CART-derived target for *S. aureus* at MIC ≤0.5 µg/mL. Lower bounds also exceed non-clinical PK-PD targets associated with bacteriostasis at MIC ≤2 µg/mL for *S. aureus* and MIC ≤1 µg/mL for *S. pneumoniae*. Bacteriostatic rather than maximal (i.e., 2-log kill) PK-PD targets may be considered, as exposures predicted in neutropenic infected animals are indicative exclusively of the drug's effect without the aid of an immune system. However, it should be noted that limited data suggests *in vivo* efficacy of ceftaroline was not greatly amplified by the presence of an immune system between neutropenic versus non-neutropenic mice infected with the same single pneumococcal strain.

Table 2.2.4.1-4 Median (90% CI) % *f*T>MIC by MIC following 600 mg Q12h in simulated patients with normal renal function and various associated PK-PD targets

MIC (µg/mL)	Median (90% CI) % *f*T>MIC	*S. aureus*				*S. pneumoniae*		
		Stasis (26%)	1-log Kill (36%)	2-log Kill (51%)	Microbiological Success (55%)	Stasis (35%)	1-log Kill (44%)	2-log Kill (51%)
0.125	100 (92.5-100)	X	X	X	X	X	X	X
0.25	100 (70.8-100)	X	X	X	X	X	X	X
0.5	82.5 (55.0-100)	X	X	X	X	X	X	X
1	63.3 (40.0-100)	X	X			X		
2	45.0 (27.5-74.6)	X						
4	25.8 (15.0-47.5)							
8	10.0 (1.25-20.0)							
16	0.00 (0.00-5.00)							
32	0.00 (0.00-0.00)							

Note1: X symbol denotes ≥90% probability of achieving requisite % *f*T>MIC based on lower bound of 90% confidence interval
Note2: Created from Module 5.3.4, Report ICPD 00174-8, Appendix 5
Note3: Created from Module 5.3.4, Report ICPD 00174-9, Appendix 5

Susceptibility Breakpoints: Based on PK-PD target attainment data alone (where desired targets were % *f*T>MIC associated with maximal efficacy or bacteriostasis from neutropenic murine thigh models or higher probabilities of per-patient microbiological success from clinical exposure-response analysis), a susceptible MIC breakpoint of 0.5-2 µg/mL is supported for *S. aureus* and 0.5-1 µg/mL for *S. pneumoniae*. Susceptibility breakpoints have historically been dependent upon bacteriostatic targets, and accordingly, an MIC breakpoint of ≤2 µg/mL for *S. aureus* and ≤1 µg/mL for *S. pneumoniae* could be established for ceftaroline based on PK-PD target attainment. PK-PD target attainment results, however, must be considered along with MIC population data as well as clinical and microbiological outcomes by pathogen and MIC from Phase 3 cSSSI and CABP trials (**Table 2.2.4.1-5**).

Current draft labeling by the Sponsor proposes a susceptibility breakpoint of (b) (4) for *S. aureus* and (b) (4) for *S. pneumoniae*. Refer to the Clinical Microbiology (A Goodwin, PhD) review for complete analysis of ceftaroline microbiology, including recommended susceptibility interpretive criteria.

Table 2.2.4.1-5 Microbiological response rates by ceftaroline MIC against *S. aureus* and *S. pneumoniae* from Phase 3 cSSSI and CABP trials, respectively

Ceftaroline MIC (µg/mL)	N	Microbiological Success *(i.e., eradication/presumed eradication)*
Phase 3 cSSSI (-06, -07)		
S. aureus		
0.06	3	3/3 (100%)
0.12	79	73/79 (92.4%)
0.25	156	149/156 (95.5%)
0.5	109	102/109 (93.6%)
1	11	11/11 (100%)
2	4	2/4 (50.0%)
Phase 3 CABP (-08, -09)		
S. pneumoniae		
≤0.015	34	29/34 (85.3%)
0.03	1	1/1 (100%)
0.12	1	1/1 (100%)

Note: Adapted from Module 2.7.2, Summary of Clinical Pharmacology Studies, Tables 4.5.1.3.2-1 & 4.5.2.3.2-1

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Exposure: An exposure-response analysis for safety was not performed by the Sponsor or the Pharmacometrics Reviewer due to the overall low frequency of adverse events. Moreover, there were no major dose-limiting adverse events that required further exploration. All patients in Phase 2/3 trials received either the proposed clinical regimen of 600 mg Q12h or the renal-adjusted regimen of 400 mg Q12h. Healthy adults in Phase 1 studies received single IV doses of 50-2000 mg and multiple IV doses of 600-1800 mg/day for 7-14 days (P903-01, 50-1000 mg and 600-1200/day; P903-02, 1500-2000 mg and 1800 mg/day). Special populations in Phase 1 studies such as elderly subjects and renally-impaired subjects received either 600 mg or 400 mg as a single IV dose. (Adolescent subjects and subjects who received IM administration were excluded from pooled Phase 1 studies.)

Treatment-Emergent Adverse Events: The most common treatment-emergent adverse events (TEAE) for ceftaroline in pooled Phase 1 studies and Phase 3 trials were gastrointestinal disorders (nausea, vomiting, diarrhea, and constipation) and headache.

In pooled Phase 1 studies, the percentage of subjects who experienced any treatment-emergent adverse event (TEAE) or discontinuation due to TEAE (DC-TEAE) were slightly greater with ceftaroline versus placebo, while there were no reports of serious adverse events (SAE) or deaths (**Table 2.2.4.2-1**).

Table 2.2.4.2-1 Overview of safety for **Phase 1** subjects who received ≥1 IV dose

	Healthy Population Studies[a] -01, -02, -04, -05, -11, -13, -14, -17, -18, -20		**Special Population Studies**[b] -02, -04, -11, -18		**Pooled Phase 1 Studies**[a] -01, -02, -04, -05, -11, -13, -14, -17, -18, -20	
	Ceftaroline (N=195)	Placebo (N=78)	Ceftaroline (N=41)	Placebo (N=0)	Ceftaroline (N=236)	Placebo (N=78)
N with						
Any TEAE	76 (39.0%)	25 (32.1%)	15 (36.6%)	–	91 (38.6%)	25 (32.1%)
Any SAE	0	0	0	–	0	0
D/C-TEAE	4 (2.1%)	1 (1.3%)	0	–	4 (1.7%)	1 (1.3%)
Deaths	0	0	0	–	0	0

[a] Healthy population includes only adult subjects who received IV ceftaroline fosamil, and excludes adolescents and subjects who received IM administration
[b] Special population includes elderly subjects and renally-impaired subjects who received IV ceftaroline fosamil
Note: Adapted from Module 5.3.5, Integrated Summary of Safety (cSSSI and CABP),Table 8.1.2-1

In Phase 3 trials, percentages of subjects with any TEAE, SAE, or DC-TEAE with ceftaroline were similar to or lower than that of comparator agents (vancomycin [VAN] plus aztreonam [AZT] for cSSSI; ceftriaxone [CRO] for CABP) (**Table 2.2.4.2-2**). Although minimal, incidence of subject death was greater for ceftaroline in Phase 3 trials for both cSSSI and CABP.

Table 2.2.4.2-2 Overview of safety for **Phase 3** subjects who received ≥1 IV dose

	cSSSI Phase 3 Trials -06, -07		**CABP Phase 3 Trials** -08, -09		**Pooled Phase 3 Trials** -06, -07, -08, -09	
	Ceftaroline (N=692)	VAN + AZT (N=686)	Ceftaroline (N=613)	CRO (N=615)	Ceftaroline (N=1305)	Comparator (N=1301)
N with						
Any TEAE	309 (44.7%)	326 (47.5%)	288 (47.0%)	281 (45.7%)	597 (45.7%)	607 (46.7%)
Any SAE	30 (4.3%)	28 (4.1%)	69 (11.3%)	72 (11.7%)	99 (7.6%)	100 (7.7%)
D/C-TEAE	21 (3.0%)	33 (4.8%)	27 (4.4%)	25 (4.1%)	48 (3.7%)	58 (4.5%)
Deaths	3 (0.4%)	0	15 (2.4%)	12 (2.0%)	18 (1.4%)	12 (0.9%)

Note: Adapted from Module 5.3.5, Integrated Summary of Safety (cSSSI and CABP),Table 8.1.1-1

When stratified by renal function, percentages of subjects who experienced at least one TEAE in Phase 3 trials were similar between ceftaroline and comparators for normal renal function (CrCL >80 mL/min) and mild (CrCL >50 to ≤80 mL/min) and moderate (CrCL >30 to ≤50 mL/min) renal impairment (**Table 2.2.4.2-3**). Phase 3 cSSSI and CABP trials allowed enrollment of patients with moderate renal impairment and were assigned to an adjusted regimen of ceftaroline fosamil 400 mg Q12h. Severe (CrCL ≤30 mL/min) renal impairment was an exclusion criterion in Phase 3 protocols, and as such, only limited numbers are available.

Table 2.2.4.2-3 Adverse events **by renal function** (CrCL in mL/min) in patients who received ≥1 IV dose of ceftaroline fosamil in **Phase 3** trials

	cSSSI Phase 3 Trials -06, -07		**CABP Phase 3 Trials** -08, -09		**Pooled Phase 3 Trials** -06, -07, -08, -09	
	Ceftaroline (N=692)	VAN + AZT (N=686)	Ceftaroline (N=613)	CRO (N=615)	Ceftaroline (N=1305)	Comparator (N=1301)
N with						
CrCL >80	568	560	305	319	873	879
CrCL >50 to ≤80	99	98	203	197	302	295
CrCL >30 to ≤50	23	26	92	89	115	115
CrCL ≤30	2	2	13	10	15	12
N with ≥1 TEAE	309 (44.7%)	326 (47.5%)	288 (47.0%)	281 (45.7%)	597 (45.7%)	607 (46.7%)
CrCL >80	248 (43.7%)	276 (49.3%)	122 (40.0%)	124 (38.9%)	370 (42.4%)	400 (45.5%)
CrCL >50 to ≤80	46 (46.5%)	35 (35.7%)	103 (50.7%)	104 (52.8%)	149 (49.3%)	139 (47.1%)
CrCL >30 to ≤50	14 (60.9%)	14 (53.8%)	55 (59.8%)	47 (52.8%)	69 (60.0%)	61 (53.0%)
CrCL ≤30	1 (50.0%)	1 (50.0%)	8 (61.5%)	6 (60.0%)	9 (60.0%)	7 (58.3%)

Note: Adapted from Module 5.3.5, Integrated Summary of Safety (cSSSI and CABP), Table 12.1.6-1

Refer to the Medical Officer's review (A Porcalla, MD) for complete analysis of ceftaroline safety.

Effect on Intestinal Microflora: Following ceftaroline fosamil 600 mg IV Q12h for 7 days in healthy adults (n=12), there was no measurable concentration of active ceftaroline (by microbiological assay) in fecal samples at any collection time point (**P903-14**). Moreover, there was no significant change in median counts of aerobic and anaerobic intestinal microflora from baseline to Day 7 (end of dosing), Day 14 (follow-up), and Day 21 (end of study) except for Enterobacteriaceae on Day 21 with increased numbers of *K. pneumoniae* in 1/12 subjects and *Citrobacter* spp. in 5/12 subjects. No new colonizing aerobes or anaerobes with ≥4-fold increased MIC of ceftaroline were also noted.

Ceftaroline appears to have minimal effect on overall intestinal microflora. However, the possibility of *Clostridium difficile* overgrowth, which can manifest into *C. difficile*-associated diarrhea (known risk for nearly all antibacterial agents) cannot be eliminated.

2.2.4.3 Does this drug prolong the QT or QTc interval?

There was no significant QT prolongation detected at the supratherapeutic dose of ceftaroline fosamil (1500 mg as single 1-hour IV infusion) in a thorough QT study of 54 healthy adults (**P903-05**). Subjects received single IV doses of ceftaroline fosamil, placebo (negative control), and moxifloxacin (positive control, 400 mg as single 1-hour IV infusion) in a randomized, double-blind, three-period crossover design with 5-day washout between doses. The largest upper bound of the two-sided 90% CI for mean difference between ceftaroline fosamil 1500 mg and placebo was below 10 msec, the threshold for regulatory concern as described in the ICH E14 Guidance (**Table 2.2.4.3-1**). The largest lower bound of the two-sided 90% CI for ΔΔQTcIb (i.e., between-treatment difference in change in QTcIb from baseline; QTcIb, QT interval corrected for heart rate using individual subject correction formula based on baseline QT-RR slope) was greater than 5 msec for moxifloxacin, indicating assay sensitivity was established.

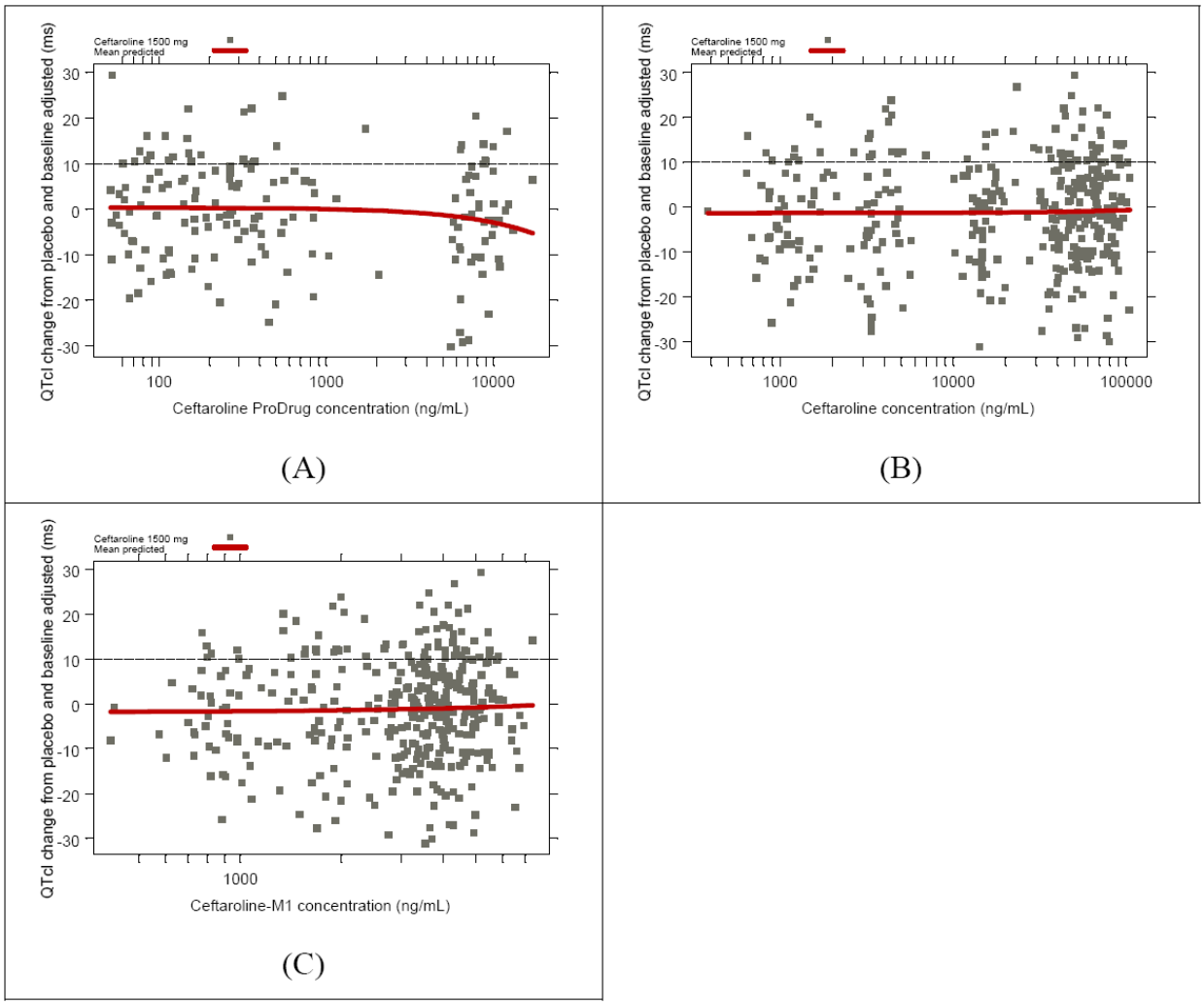
Table 2.2.4.3-1 Point estimates and 90% CI corresponding to largest upper bound for ceftaroline fosamil and largest lower bound for moxifloxacin **(IRT Analysis)**

Treatment	Time (h)	ΔΔQTcIb (msec)	90% CI (msec)
Ceftaroline fosamil 1500 mg IV	1.5	1.6	(-0.8, 4.0)
Moxifloxacin 400 mg IV*	1	19.2	(16.8*, 21.5)

* Multiple endpoint adjustment was not applied; largest lower bound after Bonferroni adjustment for four time points is 16.0 msec.

The supratherapeutic dose of ceftaroline fosamil 1500 mg produces mean ceftaroline fosamil, ceftaroline, and ceftaroline M-1 C_{max} values that are 3.0, 3.8, and 1.4 times those observed following multiple doses of the proposed therapeutic regimen of ceftaroline fosamil 600 mg Q12h in healthy adults (n=6) from **P903-01**. No exposure-response relationship was evident between ΔΔQTcIb and concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 (**Figure 2.2.4.3-1**).

Figure 2.2.4.3-1 Relationship between ΔΔQTcIb and concentrations of **ceftaroline fosamil (A)**, **ceftaroline (B)**, and **ceftaroline M-1 (C) (IRT Analysis)**



Refer to the review by the Interdisciplinary Review Team for QT Studies (IRT), dated 4 Aug 2010 for complete analysis of ceftaroline cardiovascular safety.

2.2.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dosing regimen of ceftaroline fosamil 600 mg Q12h as a 1-hour IV infusion for 5-14 days for treatment of cSSSI and 5-7 days for treatment of CABP is supported by:

- Based on PK-PD target attainment analyses, requisite exposures of ceftaroline for bacteriostasis are estimated to be achieved at MIC ≤2 µg/mL against *S. aureus* (cSSSI) and at MIC ≤1 µg/mL against *S. pneumoniae* (CABP).
- Ceftaroline $MIC_{50/90}$ against MSSA (n=1711) and MRSA (n=2254) from 2008 surveillance study of US sites was 0.25/0.25 µg/mL and 1/1 µg/mL, respectively. Appropriate MIC breakpoints will be necessary, as majority of the MRSA population reside at MIC 1 µg/mL.
- Ceftaroline $MIC_{50/90}$ against *S. pneumoniae* (n=894) from 2008 surveillance study of US sites was 0.015/0.12 µg/mL. As such, the proposed regimen is likely to achieve necessary ceftaroline exposures against the pneumococcal population.
- Clinical and microbiological efficacy in pivotal Phase 3 trials for cSSSI and CABP support the proposed regimen.
- No significant safety concerns were observed with the proposed regimen in pooled clinical studies.

Recommendations for renal-adjusted dosing by the Reviewer are different from those proposed by the Sponsor. (See **Section 2.3.2.5** for details.)

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Pharmacokinetics of ceftaroline fosamil (prodrug), ceftaroline (active), and ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline) were evaluated in healthy adults following single 1-hour IV infusions of 50, 100, 250, 500, 750, and 1000 mg **(Table 2.2.5.1-1**) and multiple 1-hour IV infusions of 300 mg Q12h for 14 days, 600 mg Q12h for 14 days, and 800 mg Q24h for 7 days (**Table 2.2.5.1-2**) (**P903-01**). Concentration-time profiles of ceftaroline and ceftaroline M-1 following single dose administration are presented in **Figure 2.2.5.1-1** and **Figure 2.2.5.1-2**, respectively. Concentration-time profiles are also shown following multiple dose administration in **Figure 2.2.5.1-3** and **Figure 2.2.5.1-4**, respectively.

Ceftaroline fosamil was quickly biotransformed to the active ceftaroline and was generally measurable only during the infusion period. (Note: Due to this rapid conversion, pharmacokinetic parameters of ceftaroline fosamil that involve proper characterization of the terminal phase were interpreted with caution.) Ceftaroline was the predominant circulating compound in plasma with ceftaroline M-1 accounting for 25-33% (based on 1st and 3rd quartiles) of ceftaroline exposure (as area under the concentration-time curve [AUC]) across single and multiple doses.

Both the maximum observed concentration (C_{max}) and AUC from time 0 to infinity (AUC_{inf}) of ceftaroline and ceftaroline M-1 increased approximately in a dose-proportional manner over the

single dose range of 50-1000 mg. Pharmacokinetic parameters of ceftaroline and ceftaroline M-1 did not vary significantly with repeat Q12h or Q24h dosing, and only minor accumulation (based on ratios of AUC over the dosing interval [AUC_{tau}]) was observed. Mean estimates of elimination half-life ($t_{1/2}$) appeared to trend higher with increasing dose but was generally 2-3 hours for ceftaroline across doses and 3.5-5 hours for ceftaroline M-1 except at 1000 mg.

Table 2.2.5.1-1 Mean ± SD pharmacokinetic parameters following **single** 1-h IV infusions of ceftaroline fosamil in healthy adults

Parameter	**50 mg (n=6)**	**100 mg (n=6)**	**250 mg (n=6)**	**500 mg (n=6)**	**750 mg (n=6)**	**1000 mg (n=6)**
Ceftaroline fosamil (prodrug)						
C_{max} (µg/mL)	0.18 ± 0.03	0.34 ± 0.16	1.12 ± 0.27	1.67 ± 0.45	3.41 ± 1.18	4.36 ± 1.02
T_{max} (h)[a]	0.33 (0.32-0.92)	0.33 (0.33-0.92)	0.50 (0.33-0.92)	0.67 (0.33-0.67)	0.33 (0.33-0.67)	0.80 (0.33-0.93)
Ceftaroline (active)						
C_{max} (µg/mL)	1.51 ± 0.25	3.08 ± 0.96	10.05 ± 1.68	16.64 ± 2.11	23.38 ± 4.92	30.49 ± 4.32
T_{max} (h)[a]	0.92 (0.90-1.08)	0.92 (0.92-1.10)	0.92 (0.92-1.25)	1.08 (0.92-1.08)	1.00 (0.92-1.08)	0.92 (0.92-1.02)
AUC_{inf} (µg*h/mL)	3.95 ± 0.73	6.72 ± 1.67	23.41 ± 5.38	44.82 ± 2.86	57.60 ± 9.75	80.89 ± 8.63
$t_{1/2}$ (h)	2.03 ± 0.15	2.23 ± 0.42	2.33 ± 0.26	2.53 ± 0.28	2.62 ± 0.29	2.90 ± 0.14
CL (L/h)	11.53 ± 2.33	13.73 ± 2.94	9.87 ± 2.35	9.89 ± 0.63	11.79 ± 2.07	11.02 ± 1.17
V_z (L)	33.35 ± 4.46	42.88 ± 4.19	32.78 ± 7.17	35.87 ± 3.45	44.40 ± 8.08	45.97 ± 5.23
Ceftaroline M-1 (open-ring metabolite)						
C_{max} (µg/mL)	0.16 ± 0.04	0.68 ± 0.10	0.72 ± 0.26	2.23 ± 0.65	2.85 ± 0.59	2.95 ± 0.36
T_{max} (h)[a]	2.24 (0.92-3.02)	0.92 (0.92-1.10)	1.25 (1.08-2.00)	1.08 (0.92-1.27)	1.08 (0.92-1.50)	0.98 (0.92-1.50)
AUC_{inf} (µg*h/mL)	1.32 ± 0.32	3.39 ± 0.72	5.88 ± 1.37	13.72 ± 1.39	19.30 ± 4.76	21.29 ± 3.57
$t_{1/2}$ (h)	3.55 ± 0.72	3.85 ± 1.15	4.04 ± 0.27	4.92 ± 1.31	4.98 ± 0.69	6.98 ± 1.65
CL (L/h)	35.95 ± 7.93	27.65 ± 4.99	40.25 ± 8.42	33.39 ± 3.06	37.26 ± 9.51	43.88 ± 8.45
V_z (L)	185.0 ± 61.6	155.3 ± 61.0	233.2 ± 44.4	239.3 ± 75.0	260.4 ± 36.2	436.2 ± 98.6
AUC_{inf} Ratio to Ceftaroline	0.34 ± 0.06	0.52 ± 0.10	0.25 ± 0.03	0.31 ± 0.02	0.33 ± 0.06	0.26 ± 0.03

[a] T_{max} expressed as median (minimum-maximum)
Note: Created from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Appendix 7A

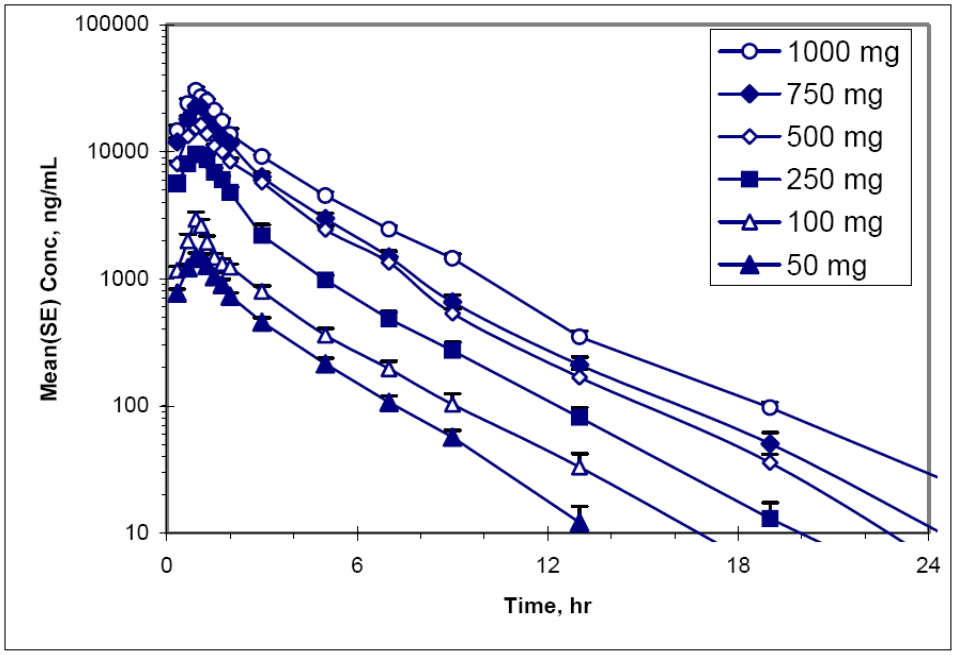
Table 2.2.5.1-2 Mean ± SD pharmacokinetic parameters following **multiple** 1-h IV infusions of ceftaroline fosamil in healthy adults

Parameter	300 mg Q12h (n=6)		600 mg Q12h (n=6)		800 mg Q24h (n=6)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 7
Ceftaroline fosamil (prodrug)						
C_{max} (µg/mL)	1.49 ± 0.33	1.44 ± 0.49	3.44 ± 1.18	3.23 ± 1.06	3.08 ± 0.47	4.16 ± 1.03
T_{max} (h)[a]	0.70 (0.67-0.92)	0.67 (0.33-0.92)	0.33 (0.33-0.67)	0.45 (0.33-0.92)	0.67 (0.32-0.97)	0.68 (0.33-0.93)
Ceftaroline (active)						
C_{max} (µg/mL)	9.98 ± 0.76	8.55 ± 1.85	18.97 ± 0.71	21.33 ± 4.10	29.66 ± 4.97	31.51 ± 2.39
T_{max} (h)[a]	1.00 (0.92-1.13)	0.92 (0.92-1.08)	1.00 (0.92-1.25)	0.92 (0.92-1.08)	0.92 (0.65-1.08)	1.08 (0.92-1.08)
C_{tr} (µg/mL)	0	0.21 ± 0.09	0	0.41 ± 0.15	0	0.02 ± 0.01
AUC_{inf} (µg*h/mL)	25.79 ± 3.84	–	56.79 ± 9.31	–	72.37 ± 8.66	–
AUC_{tau} (µg*h/mL)	–	24.32 ± 3.66	–	56.25 ± 8.90	–	74.15 ± 14.22
$t_{1/2}$ (h)	2.56 ± 0.47	2.62 ± 0.41	1.60 ± 0.38	2.66 ± 0.40	2.16 ± 0.15	2.63 ± 0.24
CL (L/h)	10.47 ± 1.62	11.10 ± 1.62	9.58 ± 1.85	9.60 ± 1.40	9.88 ± 1.13	9.86 ± 2.11
V_z (L)	38.22 ± 6.14	39.98 ± 5.05	21.97 ± 5.43	35.30 ± 7.40	30.80 ± 4.34	37.03 ± 5.45
Accumulation Ratio	–	0.98 ± 0.17	–	1.03 ± 0.12	–	1.01 ± 0.12
Ceftaroline M-1 (open-ring metabolite)						
C_{max} (µg/mL)	1.09 ± 0.20	1.27 ± 0.13	2.72 ± 0.77	3.58 ± 0.62	2.57 ± 0.27	2.97 ± 0.68
T_{max} (h)[a]	1.18 (0.97-1.50)	1.17 (1.08-2.00)	1.00 (0.67-5.00)	1.08 (0.92-1.53)	1.38 (0.92-2.00)	1.08 (0.92-1.25)
C_{tr} (µg/mL)	0	0.28 ± 0.06	0	0.67 ± 0.26	0	0.09 ± 0.02
AUC_{inf} (µg*h/mL)	7.95 ± 0.95	–	15.80 ± 3.21	–	18.13 ± 1.72	–
AUC_{tau} (µg*h/mL)	–	8.10 ± 1.16	–	18.95 ± 4.62	–	20.64 ± 3.41
$t_{1/2}$ (h)	4.62 ± 0.65	6.94 ± 1.10	3.50 ± 1.36	6.84 ± 0.59	4.04 ± 0.71	6.87 ± 0.41
CL (L/h)	34.72 ± 4.23	34.23 ± 4.69	35.63 ± 6.60	30.05 ± 6.40	40.42 ± 3.78	36.12 ± 6.39
V_z (L)	230.7 ± 37.2	256.0 ± 45.0	177.1 ± 60.5	221.5 ± 73.1	233.3 ± 32.4	338.7 ± 60.1
Accumulation Ratio	–	1.24 ± 0.14	–	1.46 ± 0.10	–	1.12 ± 0.14
AUC Ratio to Ceftaroline	0.31 ± 0.02	0.33 ± 0.03	0.28 ± 0.03	0.33 ± 0.03	0.25 ± 0.03	0.28 ± 0.04

[a] T_{max} expressed as median (minimum-maximum)

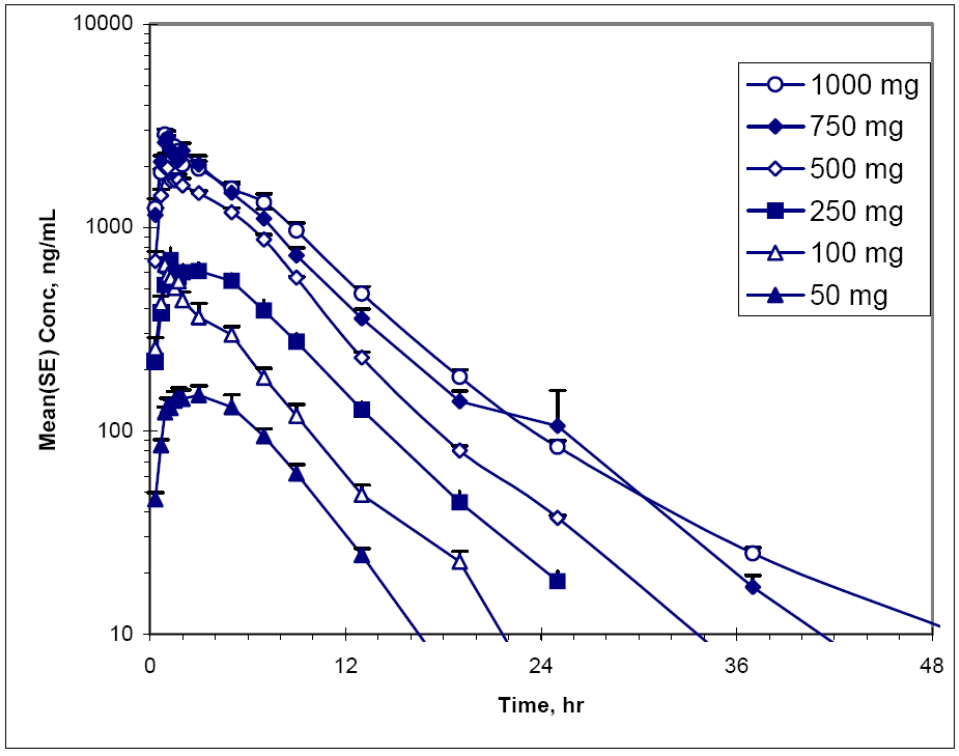
Note: Created from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Appendix 7B

Figure 2.2.5.1-1 Mean (standard error) concentration-time profiles of **ceftaroline** following **single** 1-h IV infusions of ceftaroline fosamil in healthy adults



Note: Obtained from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Figure 1

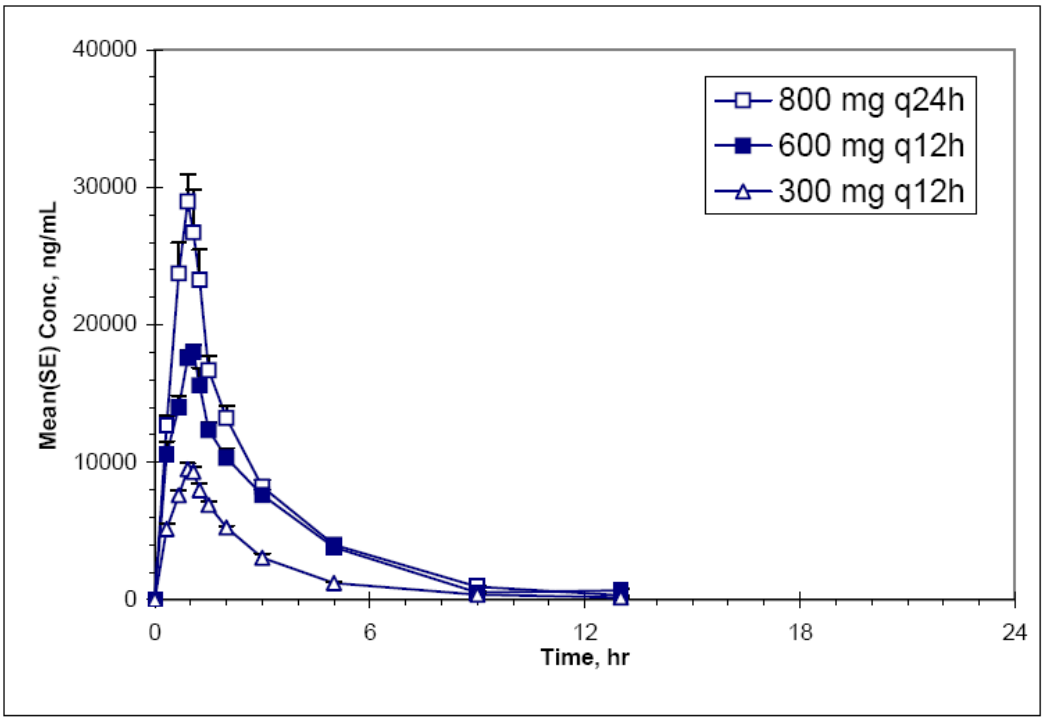
Figure 2.2.5.1-2 Mean (standard error) concentration-time profiles of **ceftaroline M-1** following **single** 1-h IV infusions of ceftaroline fosamil in healthy adults



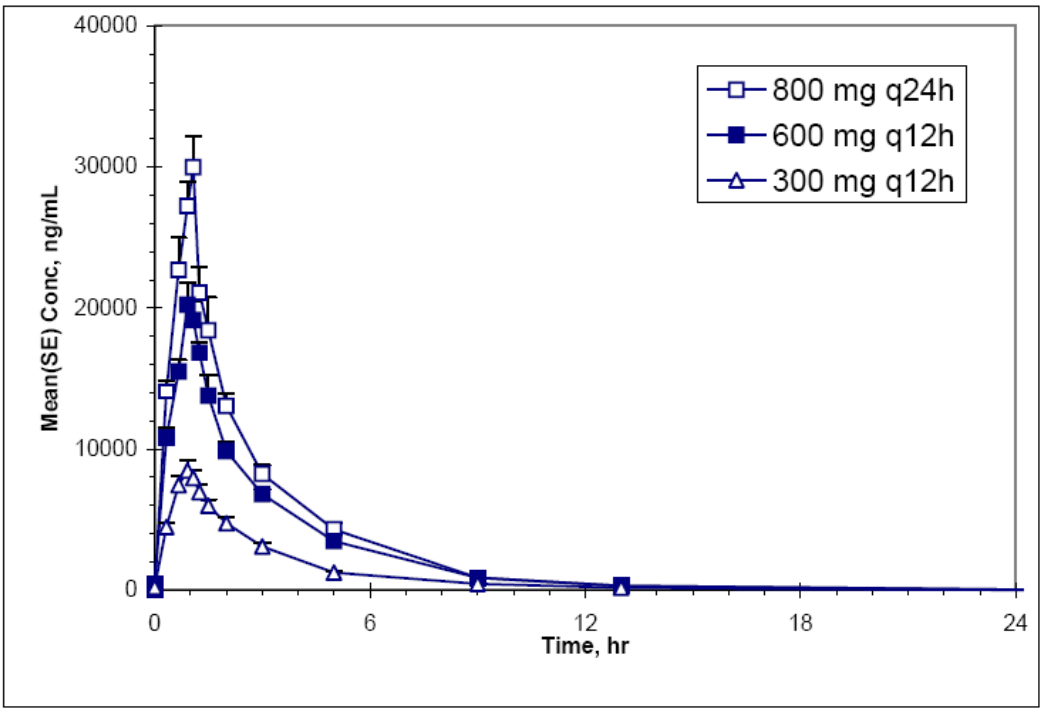
Note: Obtained from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Figure 1

Figure 2.2.5.1-3 Mean (standard error) profiles of **ceftaroline** following **multiple** 1-h IV infusions of ceftaroline fosamil in healthy adults on **Day 1 (A)** and **Day 14 or Day 7 (B)** for Q12h or Q24h regimens

(A)



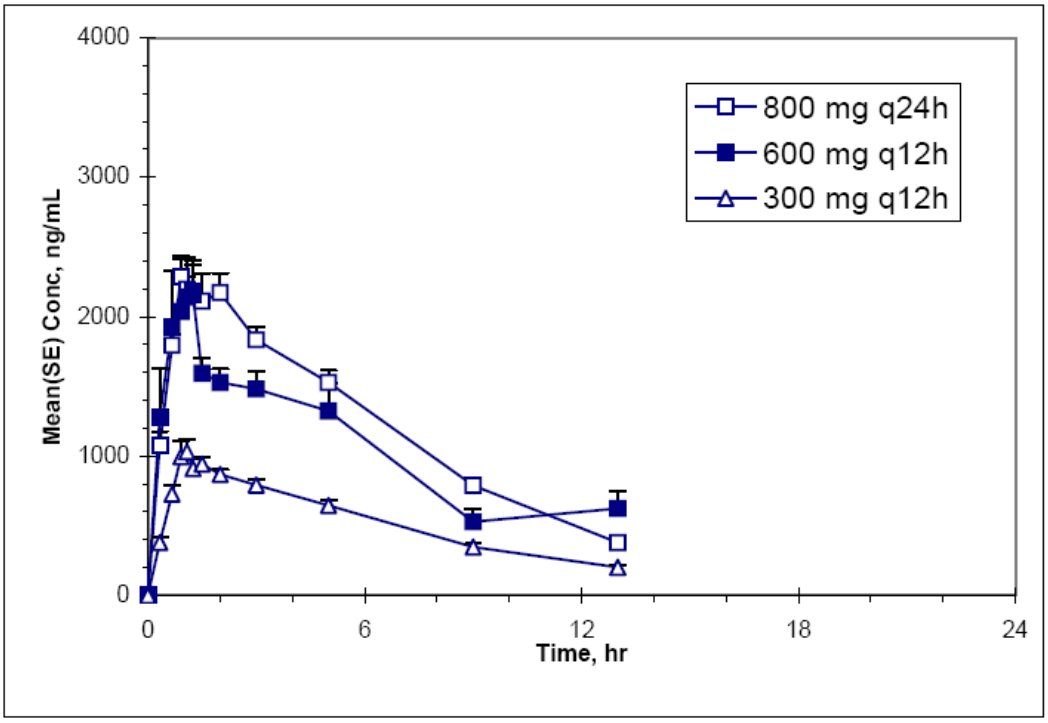
(B)



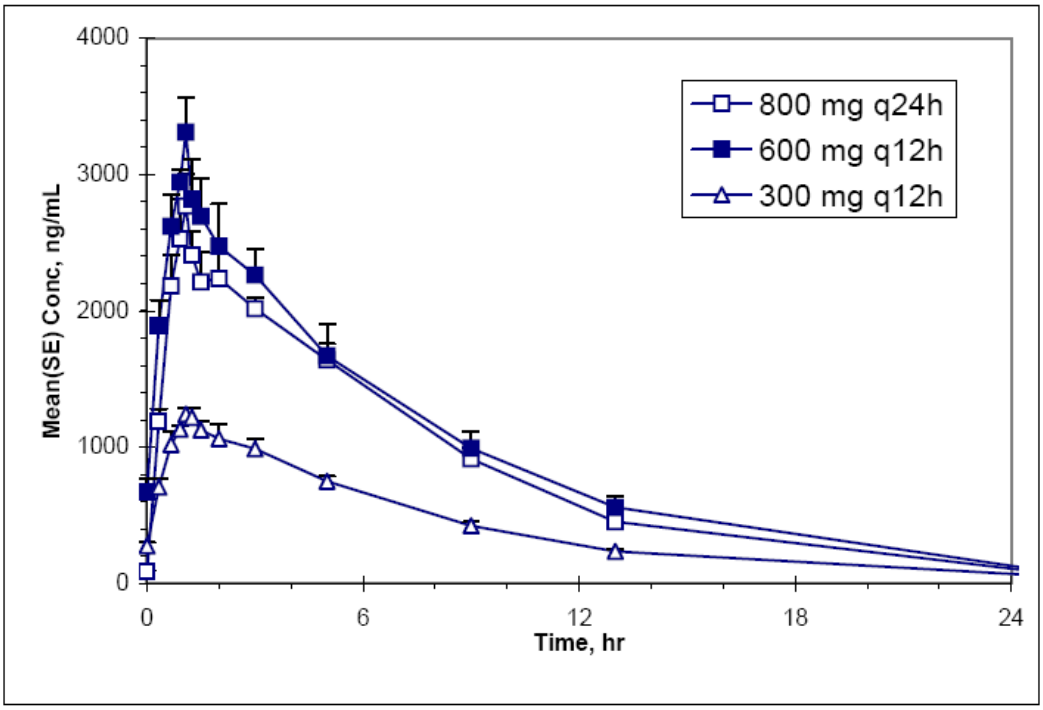
Note: Obtained from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Figure 3

Figure 2.2.5.1-4 Mean (standard error) profiles of **ceftaroline M-1** following **multiple** 1-h IV infusions of ceftaroline fosamil in healthy adults on **Day 1 (A)** and **Day 14 or Day 7 (B)** for Q12h or Q24h regimens

(A)



(B)



Note: Obtained from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Figure 4

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Assessment of covariates in population PK analysis identified age, gender, and CrCL as statistically significant predictors of ceftaroline pharmacokinetics in healthy subjects and infected patients with cSSSI or CABP. Patients with cSSSI or CABP from Phase 2/3 IV trials, who had at least one sample collected for pharmacokinetic purposes constituted the PK patient population for cSSSI (n=92) and CABP (n=127). (Note: Identified covariates were similar between the PK population and the safety population from Phase 3 trials, suggesting that pharmacokinetic results from cSSSI and CABP PK patients are representative of the complete Phase 3 patient population.) At the proposed clinical regimen of ceftaroline fosamil 600 mg Q12h, ceftaroline exposure (as steady-state AUC_{tau} derived from observed concentration data) in cSSSI and CABP PK patients differed only by 12% and 14%, respectively, from healthy subjects, while steady-state volume of distribution (V_{ss}) was comparable (**Table 2.2.5.2-1**). Because ceftaroline is primarily excreted by the kidneys, this difference in exposure can be, at least partly, attributed to differences in renal function between healthy subjects and infected patients. (See Pharmacometrics Review under **Section 4, Appendices**.)

Table 2.2.5.2-1 Comparative ceftaroline exposures in healthy subjects versus cSSSI and CABP patients following multiple 1-h IV infusions of ceftaroline 600 mg Q12h based on population PK

	Healthy Subjects (n=6) -01	**cSSSI Patients**		**CABP Patients**	
		PK Evaluable (n=92) -03, -06, -07	**Phase 3[a] (n=692)** -06, -07	**PK Evaluable[b] (n=127)** -08, -09	**Phase 3[a] (n=613)** -08, -09
Age (yr)	26.6 ± 6.2	55.4 ± 17.2	47.5 ± 17.0	57.6 ± 16.7	60.0 ± 16.9
Gender (% male)	100%	57%	64%	61%	62%
CrCL (mL/min)	117.8 ± 23.2	127.9 ± 46.0	115.7 ± 46.5	85.7 ± 35.1	80.9 ± 36.5
V_{ss} (L)	28.3 ± 1.9	30.0 ± 6.7	–	27.9 ± 10.1	–
CL (L/h)	9.7 ± 1.1	11.9 ± 3.6	–	8.8 ± 2.9	–
AUC_{tau} (µg*h/mL)	62.8 ± 7.5[c]	55.4 ± 17.2	–	71.4 ± 21.6	–

[a] Represents the safety population from Phase 3 cSSSI or CABP trials
[b] CABP PK patients included those who received dose adjustments of ceftaroline fosamil due to moderate renal impairment; there were no cSSSI PK patients who received the adjusted regimen due to moderate renal impairment
[c] AUC_{tau} for healthy subjects was estimated by population PK (not observed) from the Phase 1 study, P903-01

2.2.5.3 What are the characteristics of drug absorption?

Not applicable. Ceftaroline fosamil is intended for IV administration.

2.2.5.4 What are the characteristics of drug distribution?

Plasma protein binding of ceftaroline was assessed *ex vivo* in pooled purchased human plasma by ultrafiltration with concentrations of 1, 5, 20, and 50 µg/mL (**P0903-P-003**). Protein binding was approximately 20% with minimal decrease in mean percent bound with increasing concentration over the studied and clinically relevant range of 1-50 µg/mL (14.5-28.0%). (Plasma protein binding in the presence of renal impairment has not been evaluated for ceftaroline. However, any alteration in protein binding is not expected to significantly impact the free fraction as ceftaroline is minimally bound.)

Total radioactivity in plasma versus whole blood was evaluated in a mass balance study of healthy young adult males (n=6) following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg (**P903-13**). Plasma concentrations of total radioactivity were 1.7-2.5 times that of whole blood, suggesting minimal penetration of ceftaroline into erythrocytes.

No Phase 1 studies were performed to investigate tissue (via blister fluid or microdialysis) or intrapulmonary (via bronchoalveolar lavage) penetration of ceftaroline for the proposed indications of cSSSI and CABP.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Ceftaroline and accompanying metabolites were primarily eliminated by the kidneys in healthy young adult males (n=6) following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg (**P903-13**). Approximately 93.4% of the administered radioactive dose was recovered (up to 216 hours post-dose), with mean 87.5% of total radioactivity recovered in urine and 5.95% in feces. Approximately 64.3% of the dose was excreted in urine as unchanged ceftaroline, 2.3% as ceftaroline M-1, and 6.46% as three minor unidentified metabolites (combined). Remaining unaccounted percentages of the dose in urine were attributed to compilation of small chromatographic peaks ("background noise").

2.2.5.6 What are the characteristics of drug metabolism?

Conversion of ceftaroline fosamil to the bioactive ceftaroline appears to be mediated by *in vivo* phosphatases. Ceftaroline fosamil was consumed quickly and to near completion by 2 hours in *ex vivo* experiments with human plasma alone, while consumption was greatly reduced in human plasma stabilized with a phosphatase inhibitor (**PF04315**).

Ceftaroline M-1, the primary (but inactive) metabolite of ceftaroline, is formed by hydrolysis of the β-lactam ring of ceftaroline. The cytochrome P450 (CYP450) enzymatic system does not appear to be a significant metabolic pathway for ceftaroline, as low metabolic turnover (<12%) was observed in an *in vitro* study of pooled human liver microsomes expressing major CYP450 isoenzymes (**P0903-P-002**).

Ceftaroline fosamil, ceftaroline, ceftaroline M-1, and three minor unidentified metabolites were detected in plasma following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg in healthy young adult males (n=6) (**P903-13**). Ceftaroline was the predominant compound systemically available, followed by ceftaroline M-1, which was approximately 20% of ceftaroline AUC_{inf}. Ceftaroline fosamil was generally measurable only during IV infusion due to rapid biotransformation, and minor unidentified metabolites were present in relatively low amounts (≤0.546 μg/mL equivalent to ceftaroline fosamil).

2.2.5.7 What are the characteristics of drug excretion?

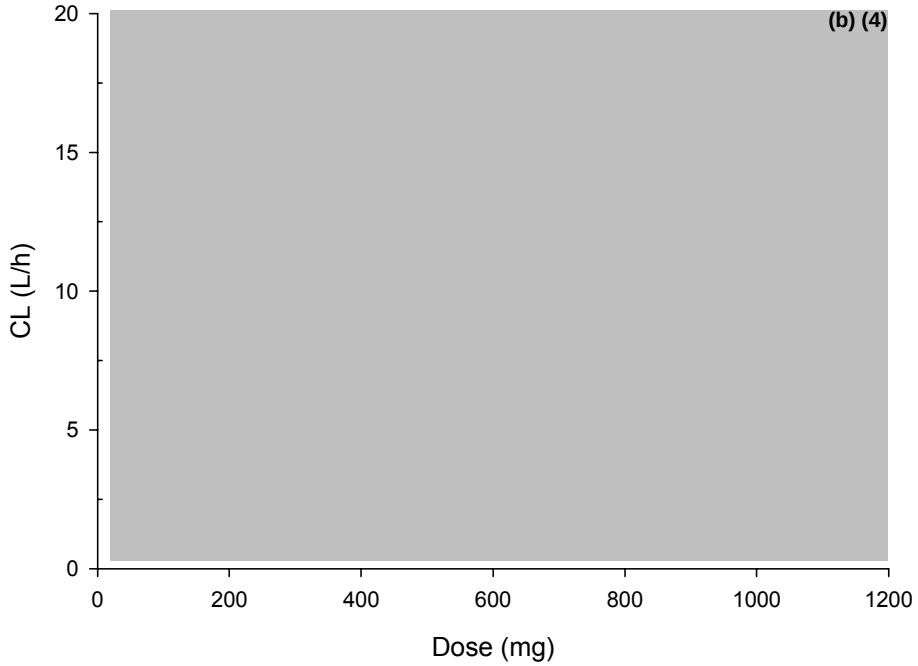
The primary route of elimination of ceftaroline and its open-ring metabolite is through renal excretion, with 64.3% of the dose recovered in urine as unchanged ceftaroline and 2.3% as

ceftaroline M-1 in healthy young adult males (n=6) following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg (**P903-13**). Alternatively, ceftaroline fosamil was not detected in urine (or feces) in any amount. Estimates of renal clearance (CL_R) accounted for 72%, on average, of total plasma clearance (CL) for ceftaroline. Mean ceftaroline CL_R of 92.67 mL/min did not exceed normal glomerular filtration rates of 90-120 mL/min, suggesting ceftaroline is predominantly eliminated by passive glomerular filtration.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

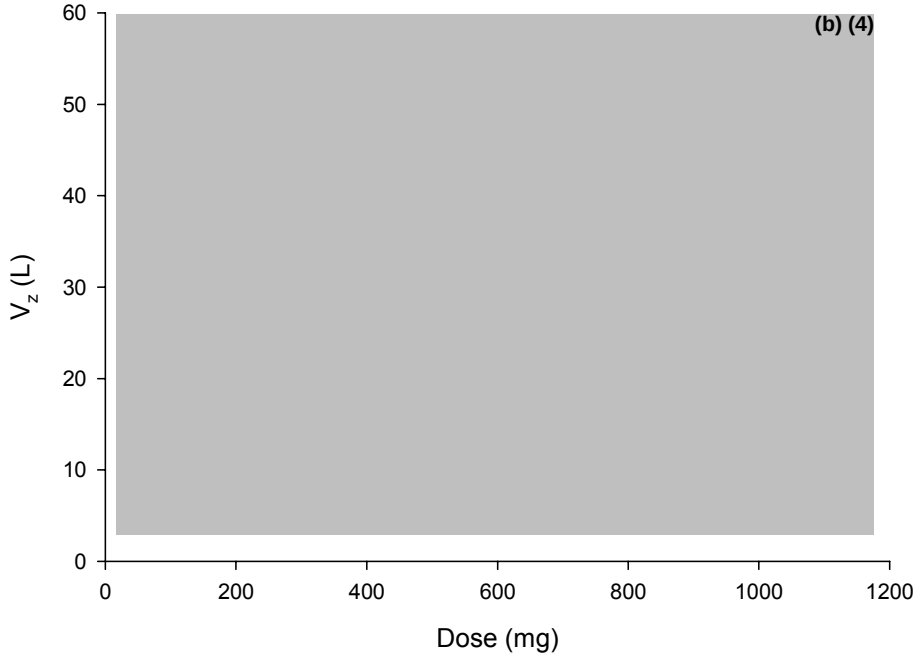
Ceftaroline and ceftaroline M-1 exhibit linear pharmacokinetics with approximately dose-proportional increase in exposure. Estimates of CL and volume of distribution of the terminal phase (V_z) for both ceftaroline (**Figure 2.2.5.8-1** and **Figure 2.2.5.8-2**, respectively) and ceftaroline M-1 (**Figure 2.2.5.8-3** and **Figure 2.2.5.8-4**, respectively) did not vary significantly with dose following single 1-hour IV infusions of ceftaroline fosamil 50-1000 mg in healthy adults (**P903-01**), except V_z for ceftaroline M-1 at the highest dose, similarly to $t_{1/2}$. (Note: Estimates of V_{ss} were not provided by the Sponsor for this study.)

Figure 2.2.5.8-1 Individual **ceftaroline CL** for single IV doses of 50-1000 mg in healthy adults



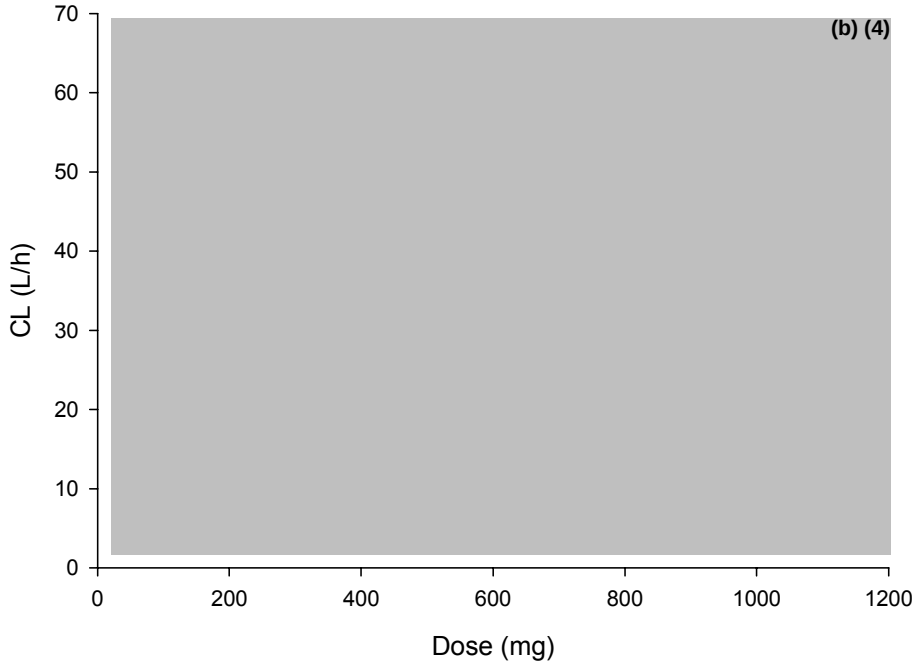
Note: Created from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Appendix 7A

Figure 2.2.5.8-2 Individual **ceftaroline V_z** for single IV doses of 50-1000 mg in healthy adults



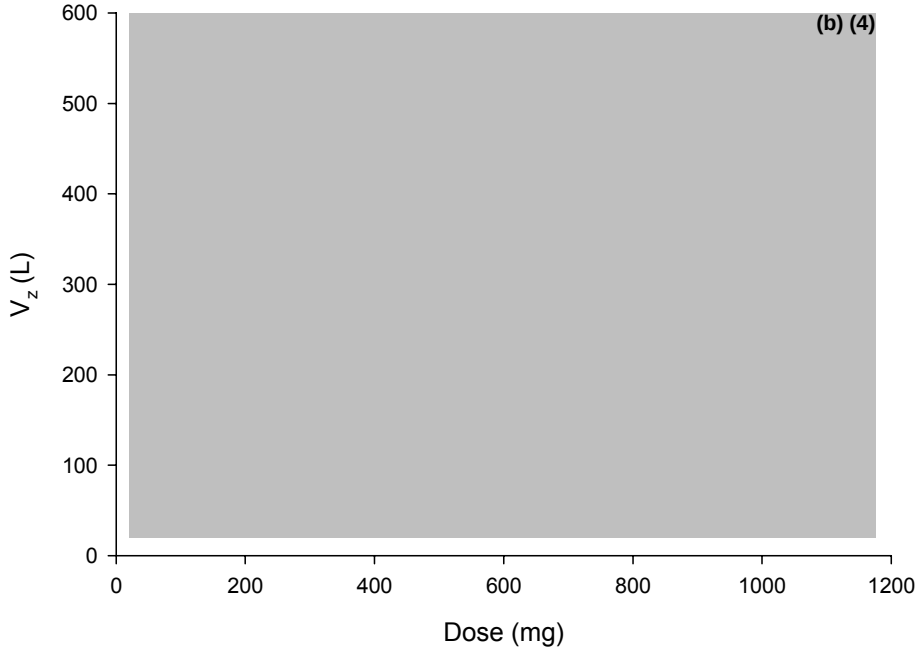
Note: Created from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Appendix 7A

Figure 2.2.5.8-3 Individual **ceftaroline M-1 CL** for single IV doses of 50-1000 mg in healthy adults



Note: Created from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Appendix 7A

Figure 2.2.5.8-4 Individual **ceftaroline M-1 V_z** for single IV doses of 50-1000 mg in healthy adults



Note: Created from Module 5.3.3, Study P903-01, Pharmacokinetic Report, Appendix 7A

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Pharmacokinetic parameters of ceftaroline and ceftaroline M-1 did not differ significantly between Day 1 and Day 14 or 7 following multiple 1-hour IV infusions of ceftaroline fosamil 300 mg Q12h for 14 days, 600 mg Q12h for 14 days, and 800 mg Q24h for 7 days in healthy adults (**P903-01**). Mean estimates $t_{1/2}$ for ceftaroline M-1 were higher with repeat dosing, however, this was likely due to extended sampling for the final versus initial dose that allowed better characterization of the terminal phase. No accumulation of ceftaroline and modest accumulation (<50%) of ceftaroline M-1 was observed and was independent of dose. (See **Table 2.2.5.1-2** under **Section 2.2.5.1** for details.)

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-subject variability, expressed as percent coefficient of variation (%CV), for ceftaroline AUC_{tau}, CL, and V_z were 16%, 15%, and 21%, respectively, in healthy subjects who received multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12h. For patients, %CV of ceftaroline AUC_{tau}, CL, volume of distribution of the central and peripheral compartments (V_c and V_p) were approximately 30%, 30%, 44%, and 21%, respectively, based on population PK analysis. Higher variability in ceftaroline pharmacokinetics (AUC_{tau} and CL) with patients compared to healthy subjects is not unexpected, as identified covariates including age and CrCL were more variable in patient populations than in healthy subjects. (See Pharmacometrics Review under **Section 4, Appendices**.) Data for evaluation of intra-subject variability were not available.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Effects of the following intrinsic factors on the pharmacokinetics of ceftaroline were evaluated in Phase 1 studies: age (elderly and adolescent), gender, and renal impairment (mild, moderate, severe, and ESRD on intermittent HD). Of these, renal impairment had the most profound effect, and accordingly, dose adjustments are warranted for patients with moderate and severe renal impairment as well as ESRD patients receiving intermittent HD.

Potential covariates including age, gender, race, and weight were also evaluated in population PK analyses. No dose adjustment is necessary for these intrinsic covariates.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative bases for the recommendation.

2.3.2.1 Elderly

Pharmacokinetics of ceftaroline and ceftaroline M-1 were evaluated in healthy elderly (≥65 years of age) subjects versus healthy young adult (18-45 years of age) subjects with equal number of males and females, following single 1-hour IV infusion of ceftaroline fosamil 600 mg (**P903-11**). Mean CL of ceftaroline and ceftaroline M-1 were 25% and 32% lower, respectively, in elderly subjects (n=16) than in young adults (n=16). Accordingly, AUC_{inf} of ceftaroline and ceftaroline M-1 were 33% and 48% greater, respectively, in the elderly cohort versus the young adult cohort (based on geometric mean ratios), while C_{max} was relatively unchanged (2% and 11% greater, respectively). Modestly higher exposures of ceftaroline and ceftaroline M-1 in elderly subjects could be attributed to decreased renal function, as median CrCL (by Cockcroft-Gault estimation) was 79.3 (61.2-106.9) mL/min for those ≥65 years old versus 125.3 (106.1-159.4) mL/min for those 18-45 years old.

In population PK analysis of cSSSI PK population (n=92), mean ceftaroline AUC_{tau} was approximately 80% higher in patients ≥65 years of age than in patients <65 years of age (95.4 versus 53.1 µg*h/mL) (**Figure 2.3.2.1-1**). However, given the small number of patients ≥65 years of age (n=5) included in this analysis, results should be interpreted with caution. For CABP PK population (n=127), mean ceftaroline AUC_{tau} was approximately 18% higher in patients ≥65 years of age than in patients <65 years of age (78.5 versus 66.8 µg*h/mL) (**Figure 2.3.2.1-2**). (Note: Doses of ceftaroline fosamil in CABP PK population also included the adjusted regimen of 400 mg Q12h for patients with moderate renal impairment. There were no cSSSI PK patients who received the adjusted regimen due to moderate renal impairment.) (See Pharmacometrics Review under **Section 4, Appendices**.)

Figure 2.3.2.1-1 Ceftaroline AUC_{tau} box plots by elderly age in **cSSSI PK population** (n=92)

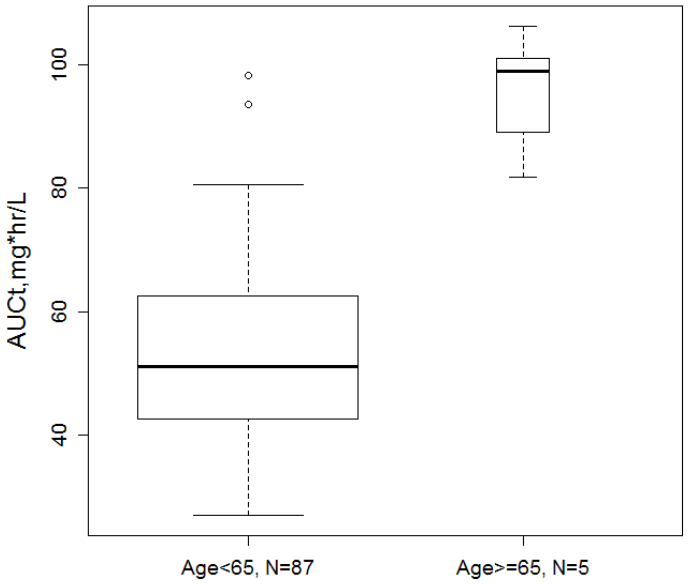
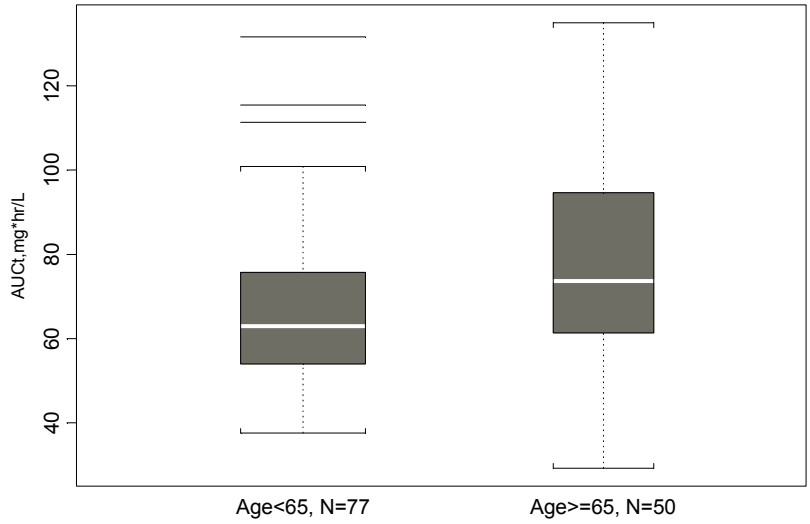


Figure 2.3.2.1-2 Ceftaroline AUC_{tau} box plots by elderly age in **CABP PK population** (n=127)



No dose adjustment is recommended based on age alone, but rather doses of ceftaroline fosamil should be adjusted according to renal function.

2.3.2.2 Pediatric patients

Pharmacokinetics of ceftaroline and ceftaroline M-1 were evaluated in hospitalized adolescent (12-17 years of age) subjects receiving antibiotic therapy, following single 1-hour IV infusion of ceftaroline fosamil 8 mg/kg for those <75 kg or 600 mg for those ≥75 kg (**P903-15**). Mean estimates of CL and V_z for ceftaroline were similar between adolescent subjects (n=7) in **P903-15** and healthy adults (n=6) in **P903-01** administered single 600 mg doses (**Table 2.3.2.2-1**). For ceftaroline M-1, however, mean estimates of CL and V_z were both 38% higher in adolescent subjects versus healthy adults. Overall, exposures trended lower in adolescents at the 8 mg/kg dose, with 10% and 54% lower mean C_{max} for ceftaroline and ceftaroline M-1, respectively, and 23% and 46% lower mean AUC_{inf}. Based on single-dose pharmacokinetic data, it appears the fixed adult dose of 600 mg would be appropriate for adolescent patients rather than the studied 8 mg/kg dose.

The Sponsor submitted a deferral request to assess ceftaroline fosamil as a Phase 4 commitment in adolescents (≥12 years to <18 years), children (≥24 months to <12 years), infants/toddlers (≥28 days to <24 months), and neonates (0 days to <28 days). Planned pediatric studies include additional pharmacokinetic studies as well as safety/efficacy trials for both cSSSI and CABP.

Table 2.3.2.2-1 Mean ± SD pharmacokinetic parameters following single 1-h IV infusion of ceftaroline fosamil in adolescents versus healthy adults

Parameter	**Adults 600 mg (n=6)** P903-01	**Adolescent 8 mg/kg (n=7)[a]** P903-15
Ceftaroline		
C_{max} (µg/mL)	18.97 ± 0.71	17.03 ± 3.63
T_{max} (h)[b]	1.00 (0.92-1.25)	0.95 (0.48-1.00)
AUC_{inf} (µg*h/mL)	56.79 ± 9.31	43.57 ± 10.11
$t_{1/2}$ (h)	1.60 ± 0.38	1.86 ± 0.17
CL (L/h)	9.58 ± 1.85	9.36 ± 2.15
V_{ss} (L)	–	25.27 ± 7.13
V_z (L)	21.97 ± 5.43	19.74 ± 6.05
Ceftaroline M-1		
C_{max} (µg/mL)	2.72 ± 0.77	1.25 ± 0.52
T_{max} (h)[b]	1.00 (0.67-5.00)	1.30 (0.92-3.00)
AUC_{inf} (µg*h/mL)	15.80 ± 3.21	8.47 ± 1.57
$t_{1/2}$ (h)	3.50 ± 1.36	3.41 ± 0.39
CL (L/h)	35.63 ± 6.60	49.13 ± 10.18
V_{ss} (L)	–	240.57 ± 53.55
V_z (L)	177.1 ± 60.5	244.8 ± 58.9

[a] Excludes 1 outlier with unusually low concentrations of ceftaroline and unusually high concentrations of M-1
[b] T_{max} expressed as median (minimum-maximum)
Note: Adapted from Module 5.3.3, Study P903-15, Table 11.2-2

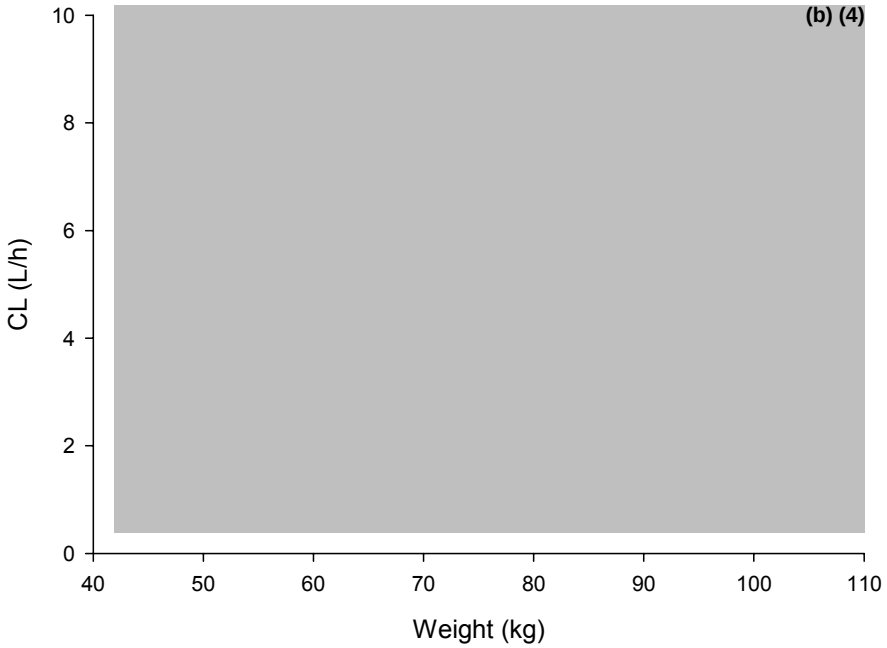
2.3.2.3 Gender

Pharmacokinetics of ceftaroline and ceftaroline M-1 were evaluated in healthy elderly males and females and healthy young adult males and females following single 1-hour IV infusion of ceftaroline fosamil 600 mg (**P903-11**). There were no significant differences in ceftaroline or ceftaroline M-1 exposures across age/gender cohorts of elderly males (n=10) versus elderly females (n=6) and young adult males (n=6) versus young adult females (n=10), although there was a trend for slightly higher C_{max} and AUC_{inf} in females. Mean C_{max} and AUC_{inf} for ceftaroline were 17% and 6-15% higher, respectively, in females versus males across age groups. For ceftaroline M-1, mean C_{max} and AUC_{inf} were 20-24% and 7-13% higher, respectively, in females versus males across age groups. For both ceftaroline and ceftaroline M-1, mean estimates of CL and V_{ss} were 6-12% and 19-24% lower, respectively, in females versus males across age groups. Modest differences in ceftaroline and ceftaroline M-1 exposure could be partly attributed to lower body weight in females, based on relationships between CL and V_{ss} with weight for ceftaroline (**Figure 2.3.2.3-1** and **Figure 2.3.2.3-2**, respectively) and ceftaroline M-1 (**Figure 2.3.2.3-3** and **Figure 2.3.2.3-4**, respectively).

In population PK analyses, no significant difference in ceftaroline AUC_{tau} was observed between male and female patients in the cSSSI PK population (n=51, 53.2 ± 16.3 µg*h/mL versus n=41, 58.1 ± 18.1 µg*h/mL) and in the CABP PK population (n=77, 69.1 ± 20.8 µg*h/mL versus n=50, 74.9 ± 22.4 µg*h/mL). (See Pharmacometrics Review under **Section 4, Appendices**.)

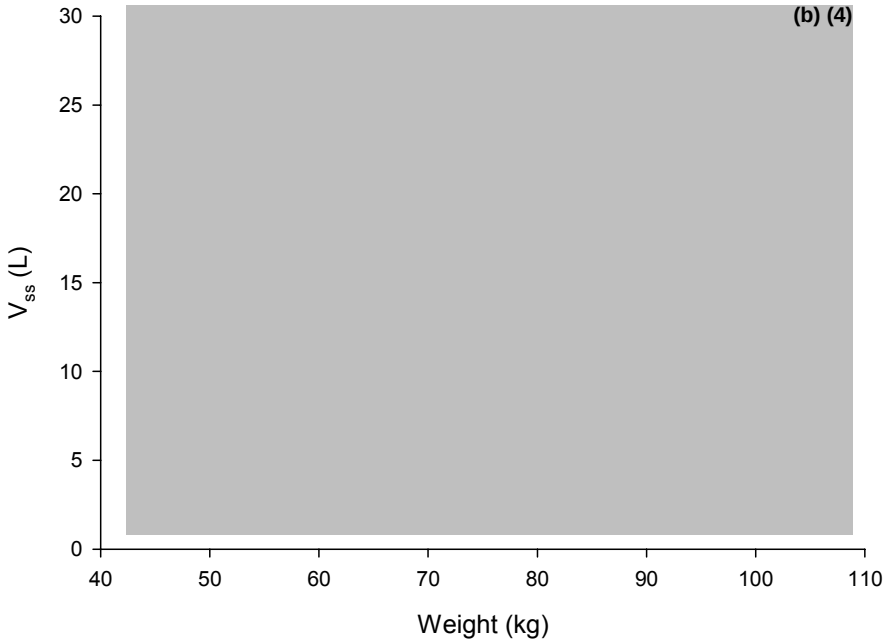
No dose adjustment based on gender is necessary.

Figure 2.3.2.3-1 Relationship between body weight and **ceftaroline CL** in healthy elderly and young adult males and females



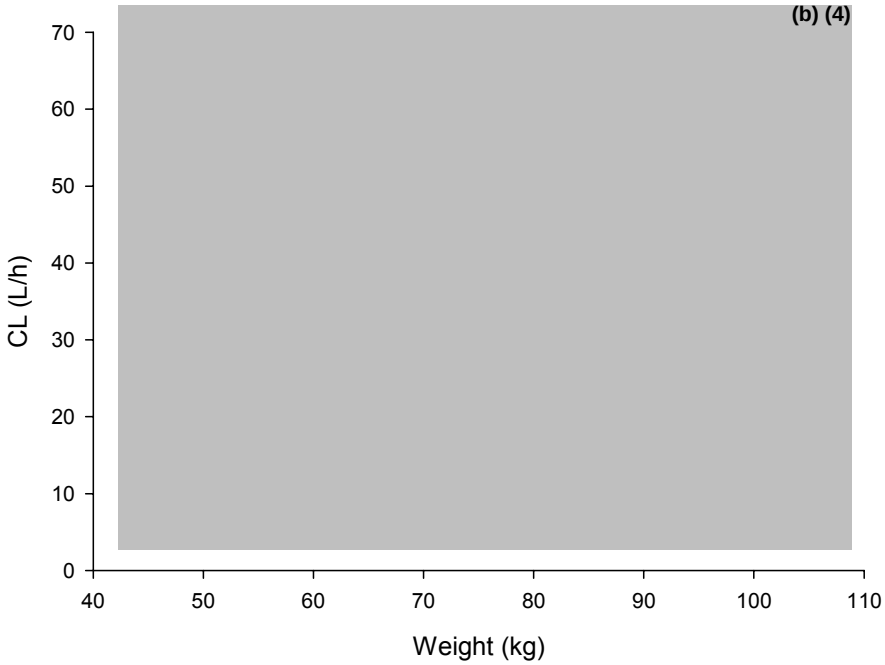
Note: Created using Module 5.3.3, Study P903-11, Tables 14.1-11, 14.1-12, & Appendix 16.2.1.2

Figure 2.3.2.3-2 Relationship between body weight and **ceftaroline V_{ss}** in healthy elderly and young adult males and females



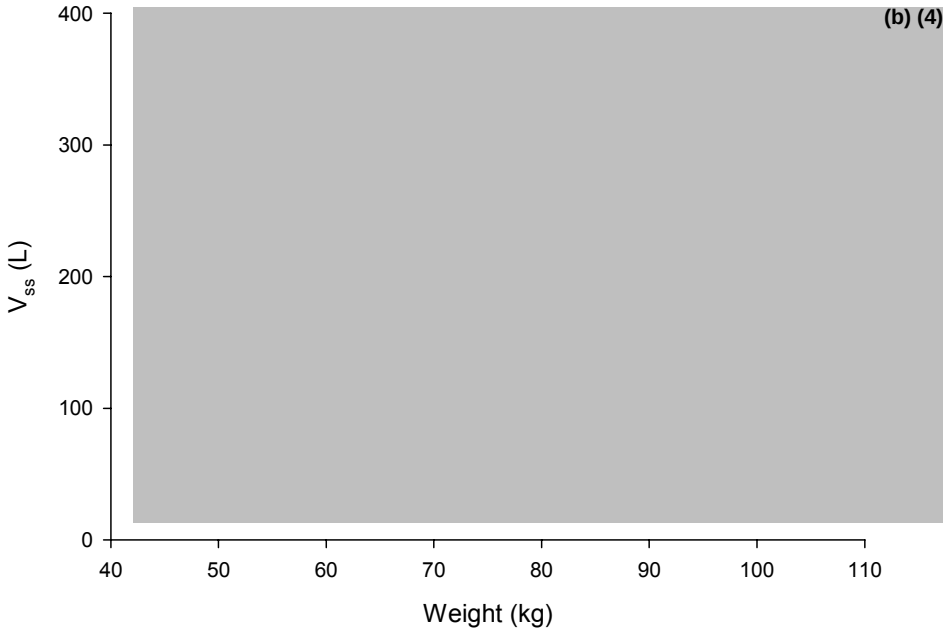
Note: Created using Module 5.3.3, Study P903-11, Tables 14.1-11, 14.1-12, & Appendix 16.2.1.2

Figure 2.3.2.3-3 Relationship between body weight and **ceftaroline M-1 CL** in healthy elderly and young adult males and females



Note: Created using Module 5.3.3, Study P903-11, Tables 14.1-15, 14.1-16, & Appendix 16.2.1.2

Figure 2.3.2.3-4 Relationship between body weight and **ceftaroline M-1 V_{ss}** in healthy elderly and young adult males and females

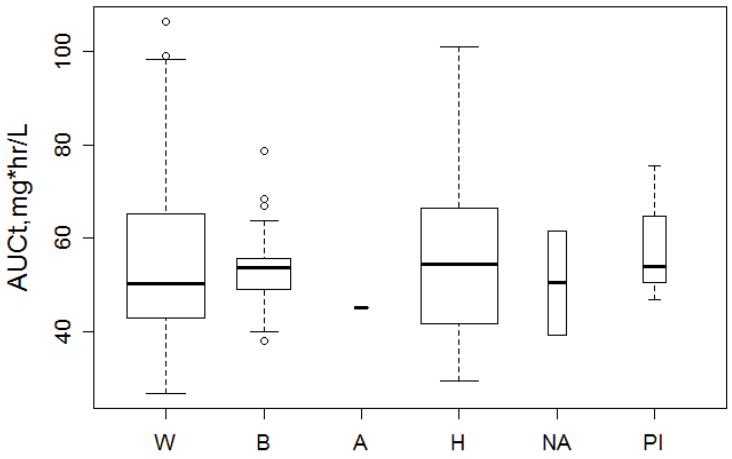


Note: Created using Module 5.3.3, Study P903-11, Tables 14.1-15, 14.1-16, & Appendix 16.2.1.2

2.3.2.4 Race

The effect of race on ceftaroline exposure was assessed in population PK analyses. In the cSSSI PK population, analysis of variance (ANOVA) of race groups indicated ceftaroline AUC_{tau} did not differ significantly between White (W, n=35), Hispanic (H, n=34), Black (B, n=17), Pacific Islander (PI, n=3), Native American (NA, n=2), and Asian (A, n=1) patients (**Figure 2.3.2.4-1**). In the CABP PK population, ceftaroline AUC_{tau} were comparable between race groups for White (n=115, 71.7 ± 21.0 µg*h/mL), Asian (n=6, 67.1 ± 31.0 µg*h/mL), and patients classified as Other (n=6, 70.0 ± 24.0 µg*h/mL). (See Pharmacometrics Review under **Section 4, Appendices**.)

Figure 2.3.2.4-1 Ceftaroline AUC_{tau} box plots by race in cSSSI PK population (n=92)



No dose adjustment based on race is necessary.

2.3.2.5 Renal impairment

Pharmacokinetics: Pharmacokinetics of ceftaroline and ceftaroline M-1 were evaluated in subjects with mild (CrCL >50 to ≤80 mL/min) and moderate (CrCL >30 to ≤50 mL/min) renal impairment (**P903-02**), severe (CrCL ≤30 mL/min) renal impairment (**P903-04**), and ESRD subjects dosed post-HD (**P903-18**) versus subjects with normal renal function (CrCL >80 mL/min) in three separate Phase 1 studies (**Table 2.3.2.5-1**). Doses of ceftaroline fosamil were administered as single 1-hour IV infusions and were the same between renally-impaired cohorts and normal counterparts within each study. (Note: CrCL, when estimated, was determined by Cockcroft-Gault calculations.)

Estimates of CL and CL_R (along with amount excreted in urine [Ae]) for ceftaroline and ceftaroline M-1 decreased with declining renal function (as CrCL) across studies (**Figure 2.3.2.5-1** and **Figure 2.3.2.5-2**, respectively). Non-renal clearance (CL_{Non-R}) did not vary with

renal impairment for ceftaroline, while estimates decreased with decreasing CrCL for ceftaroline M-1 across studies (**Figure 2.3.2.5-3**). Mean V_z and V_{ss} for ceftaroline appeared unaffected by mild or moderate renal impairment, while estimates were lower with severe renal impairment and ESRD versus normal renal function. For ceftaroline M-1, mean V_z and V_{ss} decreased with worsening renal function (i.e., from normal renal function to ESRD). Accordingly, mean $t_{1/2}$ for ceftaroline was extended from ~3 hours with normal renal function to ~6 hours with ESRD, the longest $t_{1/2}$ of all renally-impaired cohorts. When doses were administered pre-HD in ESRD subjects, approximately 21.6% of the dose was removed by the 4-hour dialysis procedure.

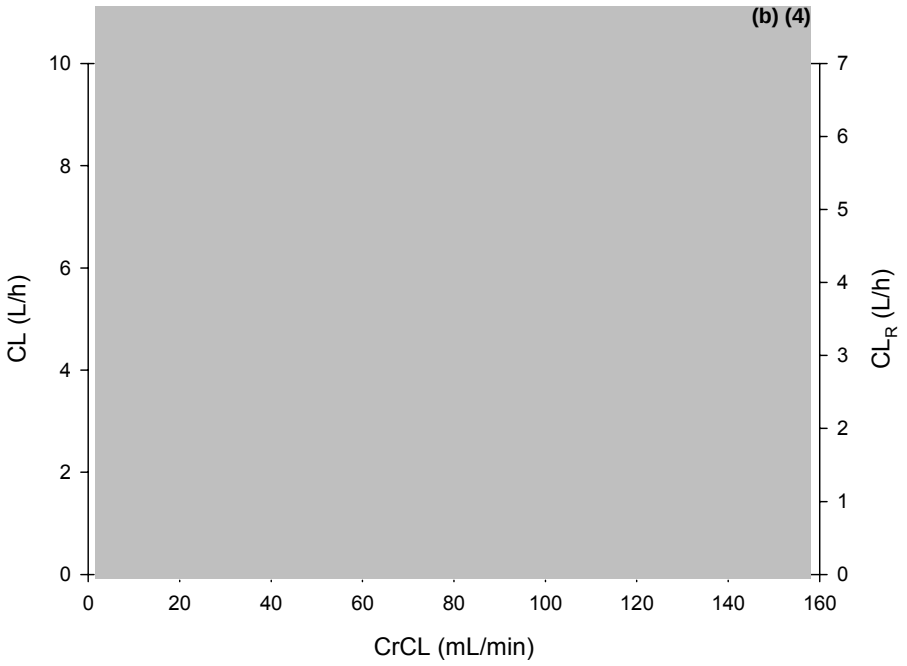
Exposures of ceftaroline and ceftaroline M-1 increased with increasing renal impairment (i.e., from normal renal function to ESRD) and are represented as C_{max} and AUC_{inf} geometric mean ratios to reference subjects with normal renal function administered the same dose in **Table 2.3.2.5-2**. Geometric mean AUC_{inf} of ceftaroline and ceftaroline M-1 were significantly greater with moderate and severe renal impairment and ESRD, while only modestly greater for mild renal impairment. Ceftaroline M-1 was impacted by impaired renal function more so than ceftaroline, and as such, mean AUC_{inf} ratios of ceftaroline M-1 to ceftaroline increased from ~0.20 with normal renal function to 0.47 with ESRD. Greater ceftaroline M-1 exposure in relation to ceftaroline is not considered to be a safety concern as similar metabolite ratios were observed in non-clinical pharmacology/toxicology studies (refer to the Pharmacology/Toxicology review [A Ellis, PhD] for details) and no apparent differences in TEAE were observed by renal impairment in pooled Phase 3 trials (see **Table 2.2.4.2-3** under **Section 2.2.4.2**).

Table 2.3.2.5-1 Mean ± SD pharmacokinetic parameters following single 1-h IV infusion of ceftaroline fosamil in subjects with mild, moderate, or severe renal impairment, and ESRD subjects on HD versus subjects with normal renal function

Parameter	P903-02			P903-04		P903-18	
	Normal 600 mg (n=6)	**Mild 600 mg (n=6)**	**Moderate 600 mg (n=6)**	**Normal 400 mg (n=6)**	**Severe 400 mg (n=6)**	**Normal 400 mg (n=6)**	**ESRD 400 mg, Post-HD (n=6)**
CrCL (mL/min)[a]	109.2 (91.7-133.8)	60.2 (51.8-71.0)	35.0 (30.1-42.5)	99.5 (80.2-139.0)	23.0 (15.0-30.0)	119.3 (101.4-168.9)	–
Ceftaroline							
C_{max} (µg/mL)	28.35 ± 6.95	28.17 ± 5.42	30.83 ± 4.86	14.75 ± 1.82	17.87 ± 2.86	16.48 ± 3.36	29.10 ± 8.49
T_{max} (h)[a]	1.00 (0.67-1.25)	0.92 (0.92-1.25)	1.13 (0.92-1.27)	1.08 (0.33-1.25)	1.25 (0.92-1.58)	0.98 (0.97-1.08)	0.98 (0.98-0.98)
AUC_{inf} (µg*h/mL)	75.56 ± 9.66	92.27 ± 25.29	114.84 ± 14.09	52.81 ± 10.51	113.32 ± 20.48	48.63 ± 9.17	128.58 ± 12.68
$t_{1/2}$ (h)	2.87 ± 0.43	3.67 ± 0.74	4.60 ± 1.11	3.02 ± 0.43	5.05 ± 1.22	2.75 ± 0.22	6.16 ± 0.81
CL (L/h)	7.11 ± 0.89	6.12 ± 1.69	4.68 ± 0.66	6.90 ± 1.44	3.22 ± 0.67	7.47 ± 1.35	2.77 ± 0.29
CL_R (L/h)	3.36 ± 0.83	1.87 ± 0.32	1.20 ± 0.38	4.38 ± 1.13	0.71 ± 0.26	4.55 ± 1.01	–
V_z (L)	29.27 ± 5.22	32.87 ± 13.31	30.48 ± 5.59	29.53 ± 3.79	22.77 ± 3.57	29.59 ± 5.05	24.58 ± 3.67
V_{ss} (L)	–	–	–	22.91 ± 3.97	20.74 ± 3.17	21.30 ± 4.32	20.69 ± 3.92
Ae (%)	46.77 ± 6.12	32.19 ± 8.29	25.83 ± 8.22	62.32 ± 4.02	22.88 ± 9.03	60.40 ± 5.98	–
Ceftaroline M-1							
C_{max} (µg/mL)	1.88 ± 0.47	2.39 ± 0.63	3.48 ± 0.61	0.97 ± 0.18	2.12 ± 0.35	0.89 ± 0.15	2.64 ± 0.93
T_{max} (h)[a]	0.92 (0.67-3.00)	1.56 (0.92-5.00)	6.91 (2.00-9.00)	1.08 (0.33-5.00)	7.05 (5.00-9.08)	4.00 (2.00-4.00)	8.00 (6.00-8.00)
AUC_{inf} (µg*h/mL)	16.93 ± 3.50	29.10 ± 9.33	54.81 ± 12.24	10.54 ± 2.38	40.34 ± 7.73	8.92 ± 2.13	60.48 ± 17.39
$t_{1/2}$ (h)	5.74 ± 0.93	6.43 ± 0.75	9.41 ± 1.79	4.40 ± 0.55	7.05 ± 1.14	4.15 ± 0.36	8.23 ± 0.70
CL (L/h)	33.66 ± 8.42	20.81 ± 8.25	10.32 ± 2.05	35.88 ± 8.10	9.31 ± 1.86	42.95 ± 11.58	6.36 ± 1.51
CL_R (L/h)	2.27 ± 0.63	1.01 ± 0.27	0.42 ± 0.24	2.47 ± 1.04	0.37 ± 0.17	2.52 ± 0.54	–
V_z (L)	271.9 ± 40.1	190.7 ± 66.8	138.1 ± 29.7	224.52 ± 39.47	93.98 ± 19.18	256.22 ± 69.36	75.97 ± 19.66
V_{ss} (L)	–	–	–	265.40 ± 38.05	130.54 ± 23.36	299.10 ± 67.29	104.59 ± 27.29
Ae (%)	6.75 ± 1.24	5.06 ± 0.98	3.96 ± 1.98	6.29 ± 1.53	3.83 ± 1.47	5.84 ± 1.22	–
AUC Ratio to Ceftaroline	0.22 ± 0.04	0.31 ± 0.04	0.48 ± 0.10	0.20 ± 0.02	0.37 ± 0.14	0.18 ± 0.02	0.47 ± 0.11

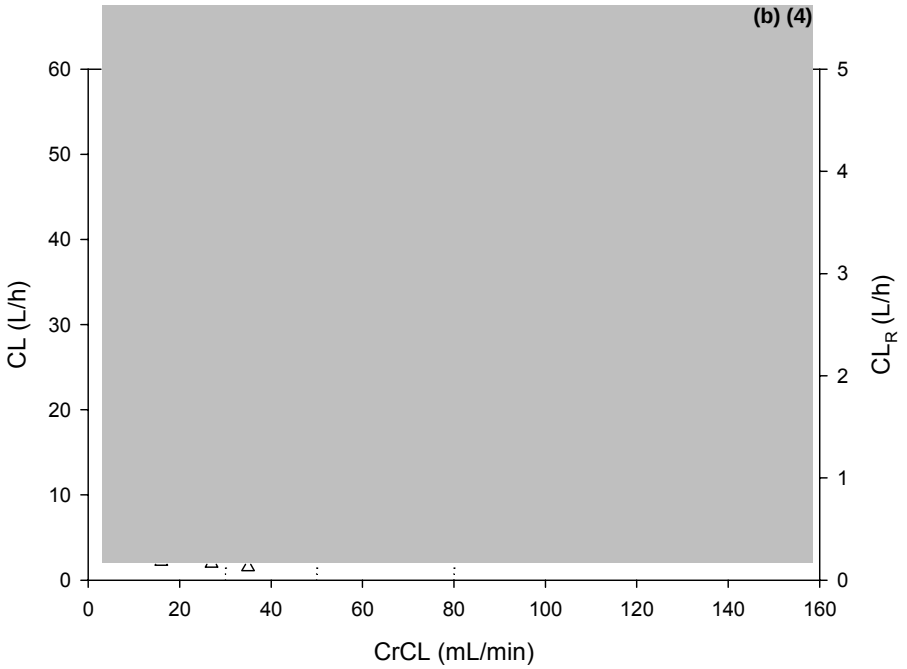
[a] CrCL and T_{max} expressed as median (minimum-maximum)
Note1: Created using Module 5.3.3, Study P903-02, Pharmacokinetic Report, Appendices 7.2 & 7.3
Note2: Created using Module 5.3.3, Study P903-04, Tables 14.1-8, 14.1-9, 14.1-26, & 14.1-27
Note3: Created using Module 5.3.3, Study P903-18, Tables 14.2-17, 14.2-18, 14.2-20, & 14.2-21

Figure 2.3.2.5-1 Relationship between **CrCL and ceftaroline CL or CL_R** following single 1-h IV infusion of ceftaroline fosamil 600 or 400 mg in subjects with normal renal function and mild, moderate, and severe renal impairment



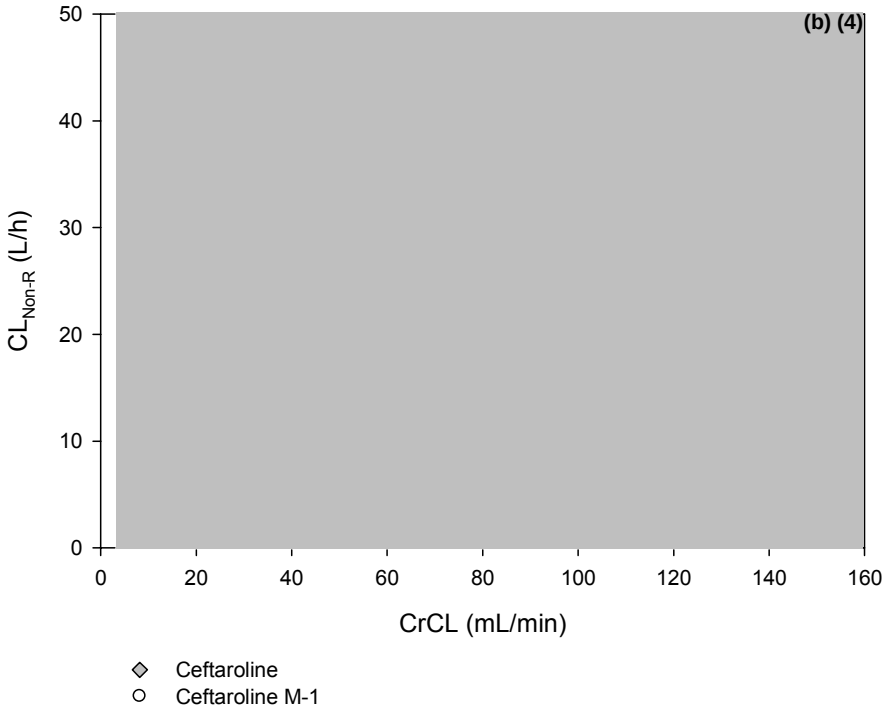
Note1: Created using Module 5.3.3, Study P903-02, Pharmacokinetic Report, Appendices 7.2 & 7.3
Note2: Created using Module 5.3.3, Study P903-04, Tables 14.1-8, 14.1-9, 14.1-26, & 14.1-27

Figure 2.3.2.5-2 Relationship between **CrCL and ceftaroline M-1 CL or CL_R** following single 1-h IV infusion of ceftaroline fosamil 600 or 400 mg in subjects with normal renal function and mild, moderate, and severe renal impairment



Note1: Created using Module 5.3.3, Study P903-02, Pharmacokinetic Report, Appendices 7.2 & 7.3
Note2: Created using Module 5.3.3, Study P903-04, Tables 14.1-8, 14.1-9, 14.1-26, & 14.1-27

Figure 2.3.2.5-3 Relationship between **CrCL and CL_{Non-R}** for ceftaroline and ceftaroline M-1 following single 1-h IV infusion of ceftaroline fosamil 600 or 400 mg in subjects with normal renal function and mild, moderate, and severe renal impairment



Note1: Created using Module 5.3.3, Study P903-02, Pharmacokinetic Report, Appendices 7.2 & 7.3
Note2: Created using Module 5.3.3, Study P903-04, Tables 14.1-8, 14.1-9, 14.1-26, & 14.1-27

Table 2.3.2.5-2 Exposure point estimates of subjects with mild, moderate, and severe renal impairment and ESRD subjects to subjects with normal renal function

Parameter	Geometric Mean Ratio			
	Mild (n=6) P903-02	**Moderate (n=6)** P903-02	**Severe (n=6)** P903-04	**ESRD, Post-HD (n=6)** P903-18
Ceftaroline				
C_{max} (µg/mL)	1.00	1.10	1.21	1.74
AUC_{inf} (µg*h/mL)	1.19	1.52	2.15	2.67
Ceftaroline M-1				
C_{max} (µg/mL)	1.26	1.88	2.20	2.86
AUC_{inf} (µg*h/mL)	1.67	3.24	3.85	6.74

Note1: Created using Module 5.3.3, Study P903-02, Pharmacokinetic Report, Tables 4.2 & 4.3
Note2: Created using Module 5.3.3, Study P903-04, Tables 11.2-1 & 11.2-4
Note3: Created using Module 5.3.3, Study P903-18, Tables 11.3-1 & 11.3.2-1

Dose Adjustment by Renal Function: Pharmacokinetic simulations were conducted to derive renal-adjusted dosing regimens based on matching exposures of the active compound, ceftaroline, by steady-state AUC_{tau} and %*f*T>MIC to that of subjects with normal renal function receiving the proposed clinical regimen of ceftaroline fosamil 600 mg Q12h as a 1-hour IV infusion.

(By Reviewer, two-compartmental analysis): Steady-state exposures of ceftaroline were simulated using individual pharmacokinetic data of subjects with moderate (**P903-02**) or severe (**P903-04**) renal impairment and ESRD subjects (**P903-18**) dosed post-HD against that of subjects with normal renal function from Phase 1 renal impairment studies. Pharmacokinetic simulations were not performed for subjects with mild renal impairment due to minimal differences in ceftaroline exposure compared to those with normal renal function, indicating 600 mg Q12h as an appropriate regimen for mild renal impairment.

Of simulated regimens (as 1-hour IV infusions), 400 mg Q12h was most suitable for moderate renal impairment, 300 mg Q12h for severe renal impairment, and 200 mg Q12h for ESRD dosed post-HD in approximating similar ceftaroline AUC over 24 hours (AUC_{24}) to those with normal renal function (**Figure 2.3.2.5-4**). Moreover, simulated % *f*T>MIC (assuming 20% protein binding for all subjects) were similar between renally-impaired subjects and subjects with normal renal function within each study (**Figure 2.3.2.5-5**). For ESRD dosed post-HD, 200 mg Q12h was favored over 400 mg Q24h in order to best maximize the time-dependent behavior of ceftaroline and additionally, no significant level of exposure was further gained with 250 mg Q12h.

Figure 2.3.2.5-4 Individual steady-state **ceftaroline AUC_{24}** of ceftaroline fosamil regimens in subjects with moderate or severe renal impairment, or ESRD dosed post-HD versus subjects with normal renal function **(simulated by Reviewer)**

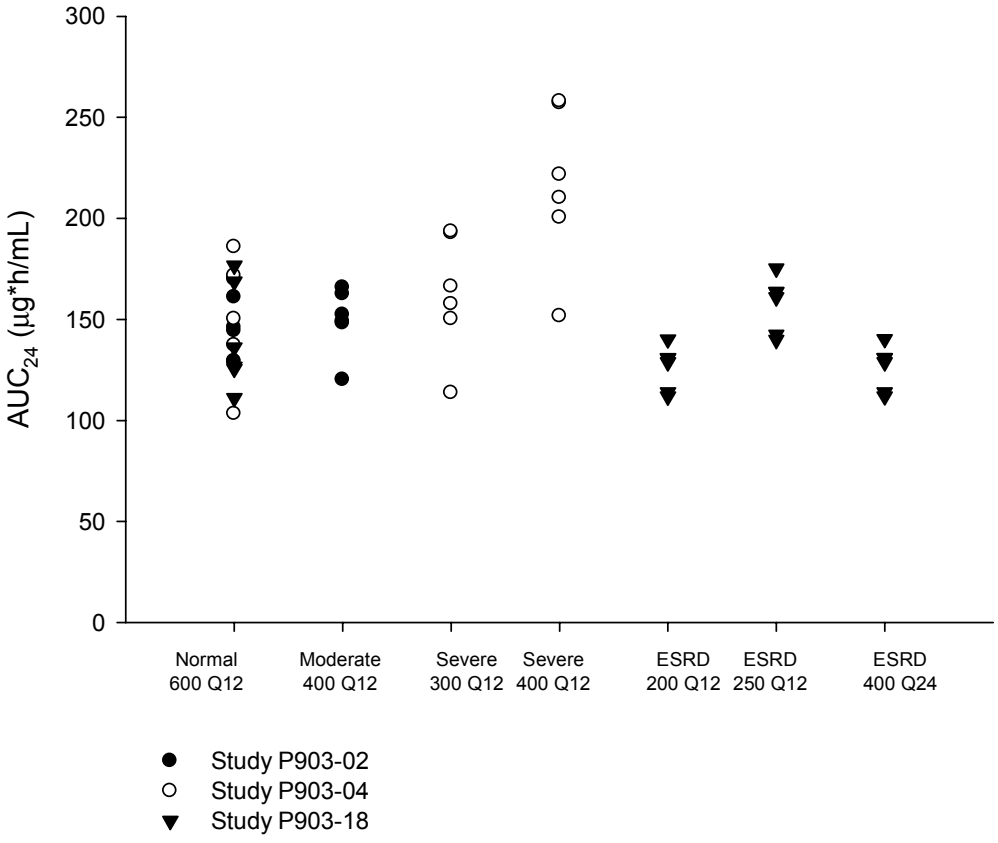
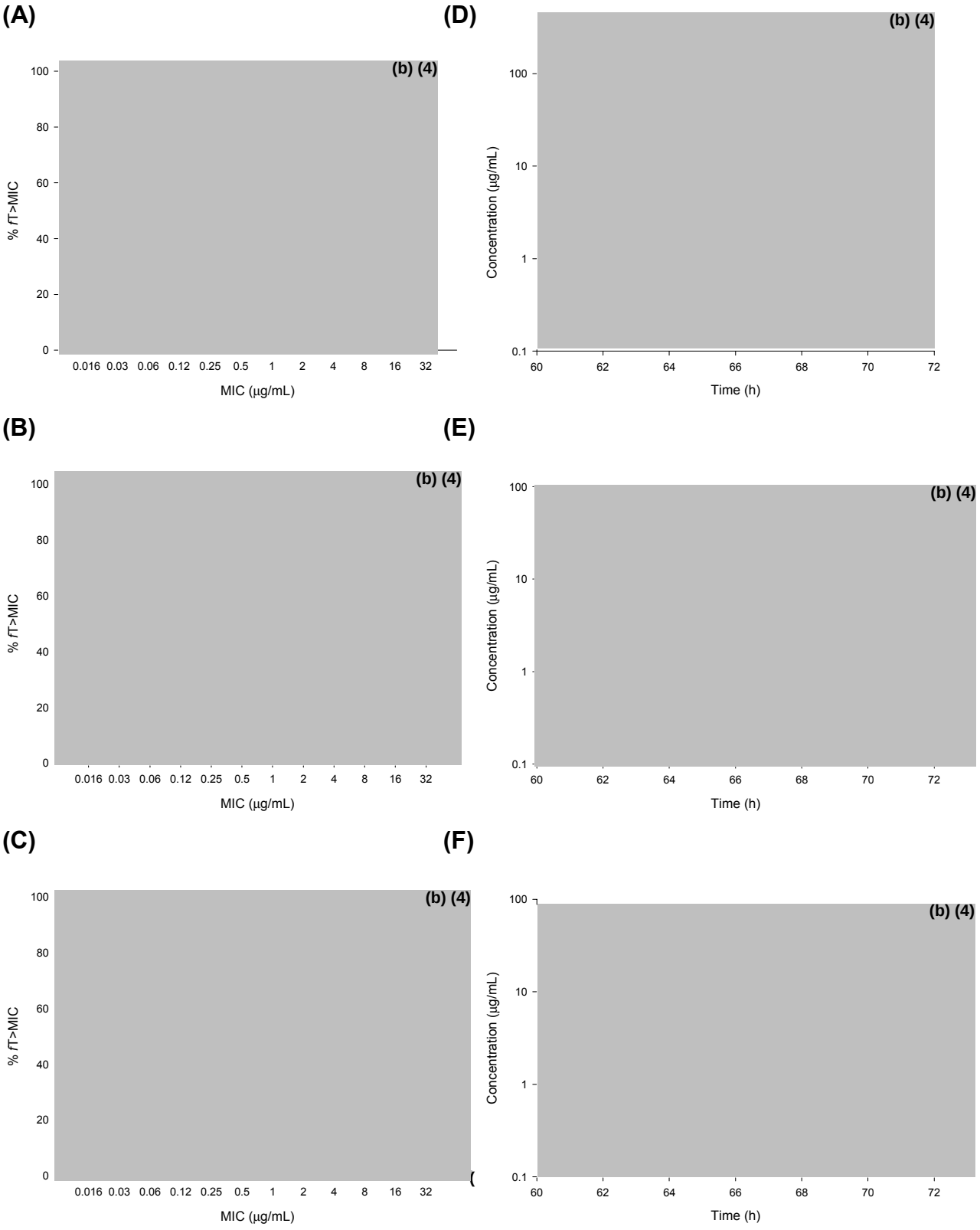
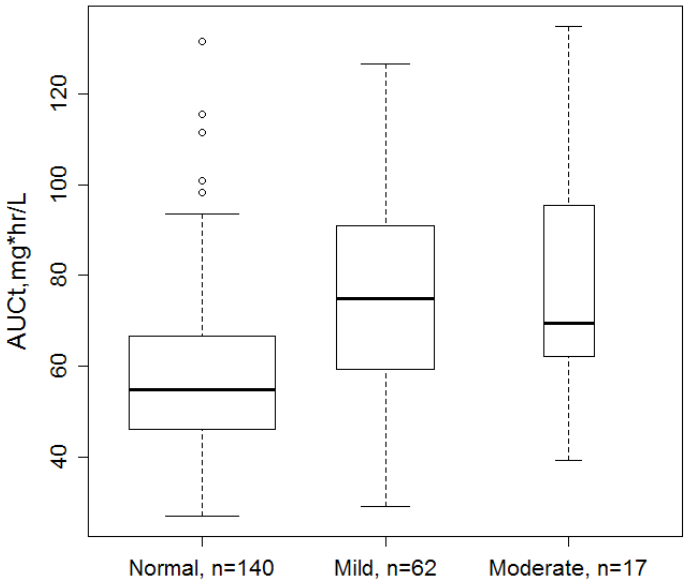


Figure 2.3.2.5-5 Individual steady-state **ceftaroline % *f*T>MIC and profiles** of ceftaroline fosamil regimens in subjects with **moderate (A and D)** or **severe (B and E)** renal impairment, or **ESRD dosed post-HD (C and F)** versus subjects with normal renal function **(simulated by Reviewer)**



Appropriateness of the 600 mg Q12h regimen for mild renal impairment and the adjusted 400 mg Q12h regimen for moderate renal impairment was verified in Phase 2/3 cSSSI and CABP IV trials (which incorporated these proposed renal dosing schemes), as indicated by observed AUC_{tau} values (by population PK estimation) of ceftaroline (**Figure 2.3.2.5-6**).

Figure 2.3.2.5-6 Ceftaroline AUC_{tau} box plots of ceftaroline fosamil 600 mg Q12h in cSSSI and CABP PK patients with normal renal function or mild renal impairment and 400 mg Q12h in cSSSI and CABP PK patients with moderate renal impairment (estimated by population PK)

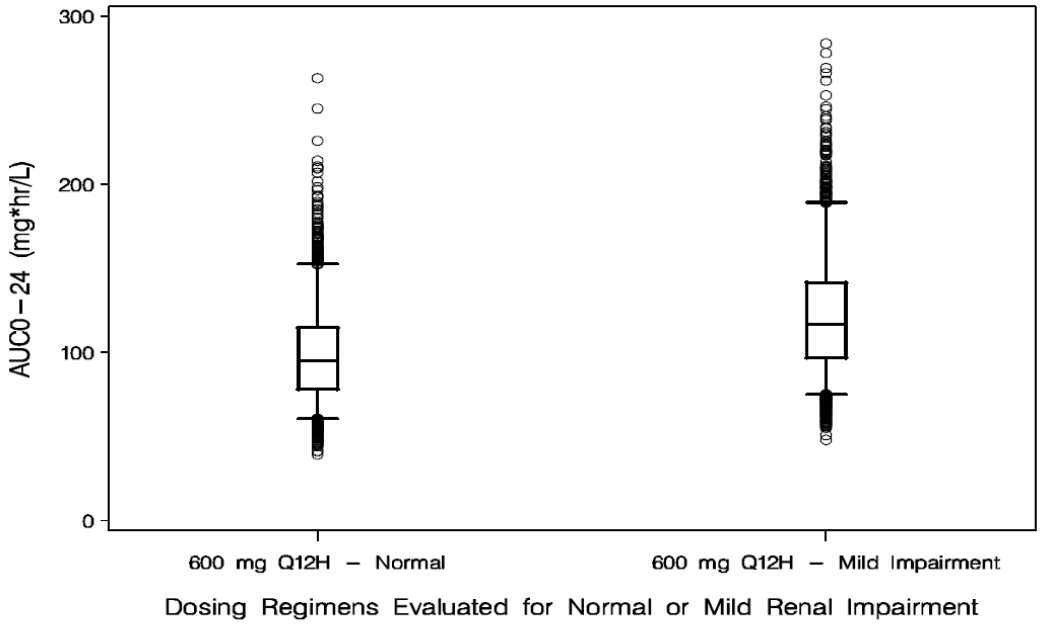


(By Sponsor, Monte Carlo simulation): Population PK models were developed using data obtained from Phase 1 studies including renal impairment studies and Phase 2/3 cSSSI and CABP trials, which incorporated the adjusted 400 mg Q12h regimen for patients with moderate renal impairment. An 8000-patient (2000 patients per renal function category) Monte Carlo simulation was performed using described population PK models for various regimens in mild, moderate, and severe renal impairment and are portrayed as comparative box plots of steady-state AUC_{24} in **Figure 2.3.2.5-7**, **Figure 2.3.2.5-8**, and **Figure 2.3.2.5-9**, respectively. Monte Carlo simulation assumptions included *(i)* uniform distribution of CrCL for each renal function category except normal renal function, for which CrCL was assigned to Gaussian distribution with mean ± SD of 118 ± 30.8 based on actual data from Phase 2/3 cSSSI patients, *(ii)* equal distribution of males and females, and *(iii)* Gaussian distribution of age within each gender category with mean ± SD of 46.2 ± 16.6 based on actual data from Phase 2/3 cSSSI patients. Monte Carlo simulation was not performed for ESRD patients on intermittent HD.

Monte Carlo simulation supports ceftaroline fosamil regimens of 600 mg Q12h for mild renal impairment and 400 mg Q12h for moderate renal impairment, while results are discordant from the Reviewer's pharmacokinetic simulations for severe renal impairment. Based on Monte Carlo

simulation data, the Sponsor proposes [redacted] (b) (4) (instead of 300 mg Q12h proposed by the Reviewer) for severe renal impairment.

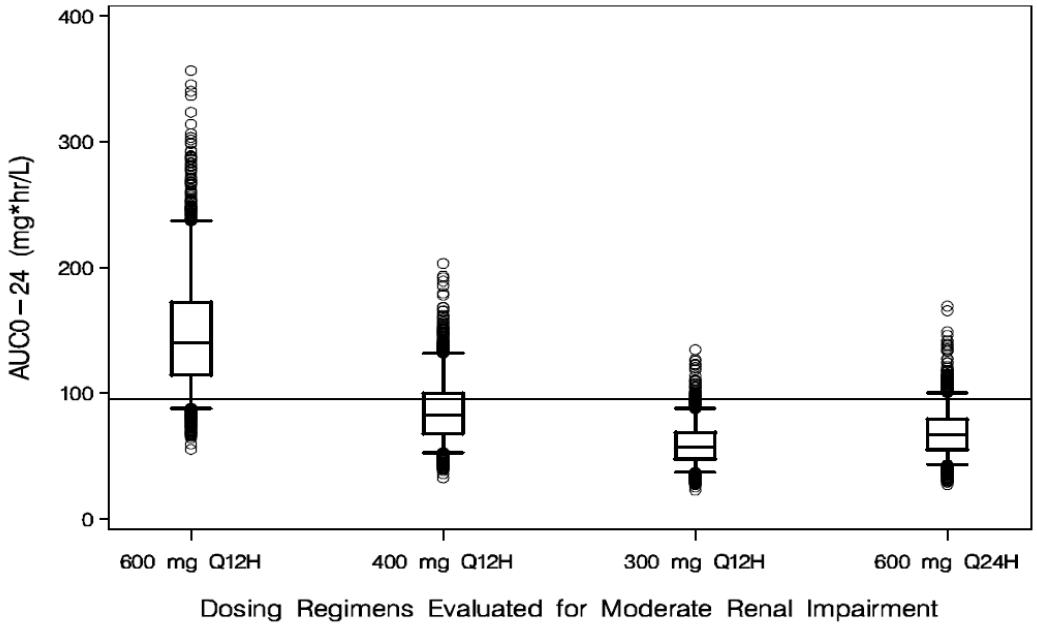
Figure 2.3.2.5-7 Ceftaroline AUC_{24} box plots of ceftaroline fosamil 600 mg Q12h in patients with **mild renal impairment** versus patients with normal renal function **(Monte Carlo simulation by Sponsor)**



Box represents the 25th and 75th percentiles, whiskers extend from the 5th to 95th percentiles

Note: Obtained from Module 5.3.4, ICPD 00174-8 or 00174-9, Figure 4-1

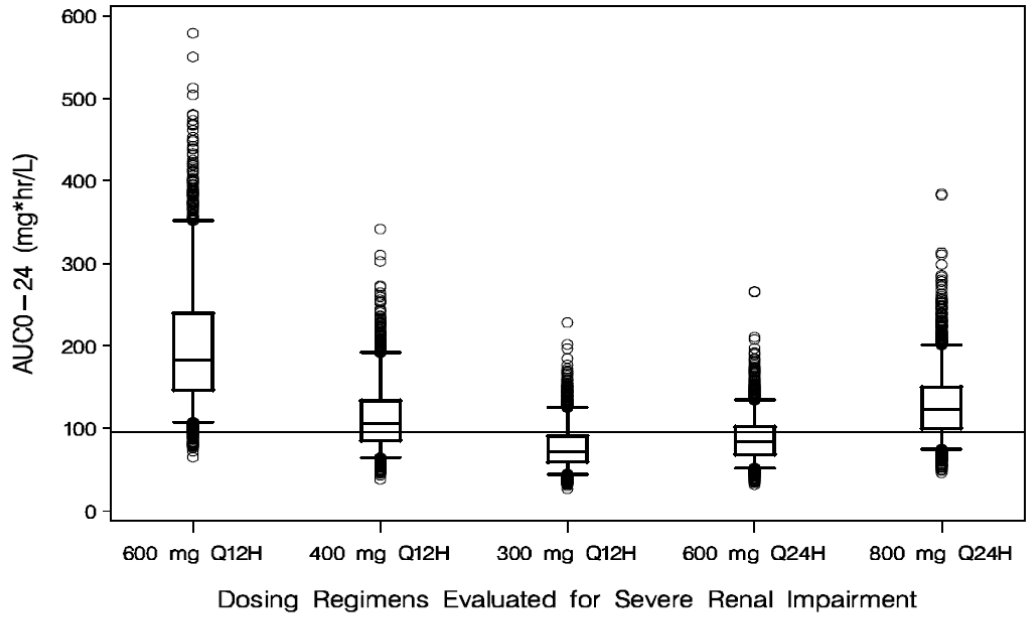
Figure 2.3.2.5-8 Ceftaroline AUC_{24} box plots of ceftaroline fosamil regimens in patients with **moderate renal impairment** versus ceftaroline fosamil 600 mg Q12h in patients with normal renal function (as solid line) **(Monte Carlo simulation by Sponsor)**



Box represents the 25th and 75th percentiles, whiskers extend from the 5th to 95th percentiles
Reference line represents the median AUC0 – 24 value for patients with normal renal function

Note: Obtained from Module 5.3.4, ICPD 00174-8 or 00174-9, Figure 4-2

Figure 2.3.2.5-9 Ceftaroline AUC_{24} box plots of ceftaroline fosamil regimens in patients with **severe renal impairment** versus ceftaroline fosamil 600 mg Q12h in patients with normal renal function (as solid line) **(Monte Carlo simulation by Sponsor)**



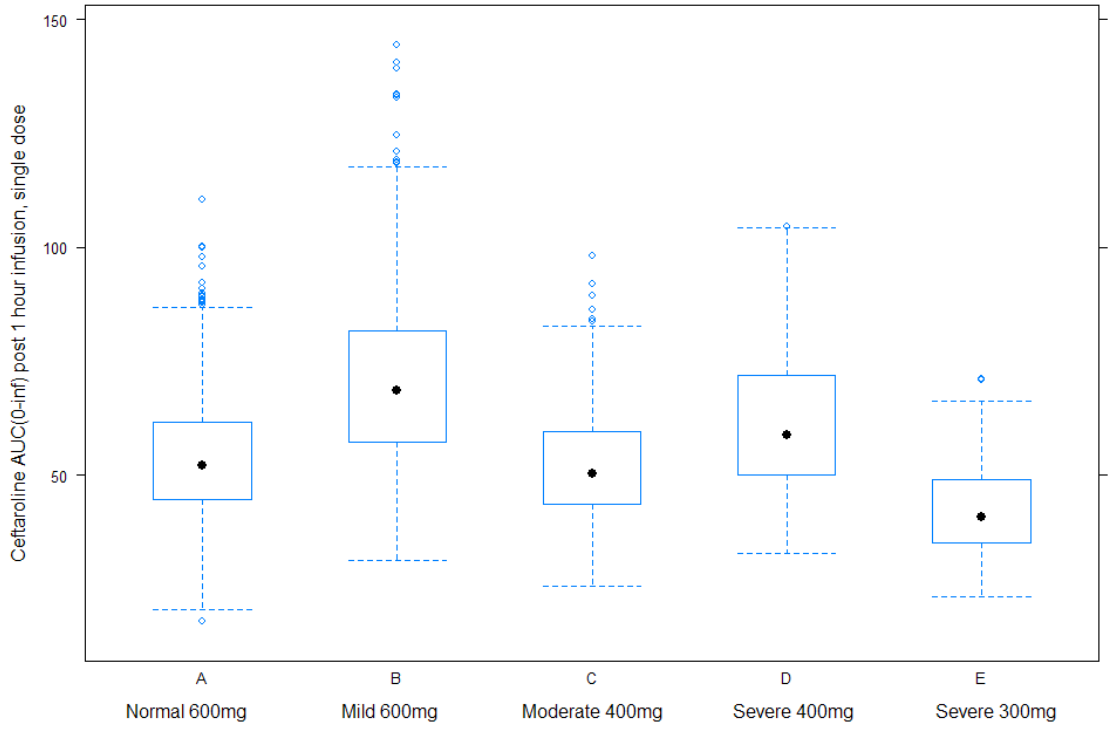
Box represents the 25th and 75th percentiles, whiskers extend from the 5th to 95th percentiles
Reference line represents the median AUC0 – 24 value for patients with normal renal function

Note: Obtained from Module 5.3.4, ICPD 00174-8 or 00174-9, Figure 4-3

(By Pharmacometrics Reviewer, population PK simulation): In light of discordant results (particularly for severe renal impairment) between the Reviewer's simulations using data from Phase 1 renal impairment studies and the Sponsor's Monte Carlo simulation using population PK from all clinical studies, the Pharmacometrics Reviewer performed an independent pharmacokinetic simulation using a population PK approach. Ceftaroline AUC_{inf} was simulated for various single 1-hour IV infusions of ceftaroline fosamil in a total of 2000 patients using demographics from CABP PK patients, which included patients with mild or moderate renal impairment, and Phase 1 subjects with severe renal impairment (**P903-04**) and are pictured as comparative box plots in **Figure 2.3.2.5-10**. Population PK simulation assumed no accumulation of ceftaroline concentrations with multiple dose administration, such that single dose AUC_{inf} was assumed to be predictive of steady-state AUC_{tau}. (Note: Only a limited number of patients with severe renal impairment were enrolled in Phase 2/3 cSSSI and CABP IV trials, of which none had pharmacokinetic data obtained.) (See Pharmacometrics Review under **Section 4, Appendices**.)

Population PK simulation by the Pharmacometrics Reviewer confirms the Sponsor's Monte Carlo simulation in that (b) (4) appears to a suitable regimen (alternatively to 300 mg Q12h proposed by the Reviewer) for severe renal impairment.

Figure 2.3.2.5-10 Ceftaroline AUC_{inf} box plots of ceftaroline fosamil doses in patients with mild, moderate, or severe renal impairment versus patients with normal renal function **(Population PK simulation by Pharmacometrics Reviewer)**



Summary of Recommendations: The Reviewer recommends 600 mg Q12h for mild renal impairment and 400 mg Q12h for moderate renal impairment, in agreement with the Sponsor's proposals. For severe renal impairment, however, the Reviewer recommends 300 mg Q12h instead of the Sponsor's proposed (b) (4). Regarding ESRD, (b) (4) the Reviewer recommends 200 mg Q12h, to be dosed post-HD on HD days for patients receiving intermittent dialysis. (Note: Recommendations by the Reviewer were determined using pharmacokinetic data from Phase 1 renal impairment studies.)

Despite verification of the Sponsor's Monte Carlo simulation results by the Pharmacometrics Reviewer, it appears simulated ceftaroline AUC_{tau} are underestimates when compared to observed values from cSSSI and CABP PK patients for mild and moderate renal impairment, while comparable for normal renal function (**Table 2.3.2.5-3**). In turn, observed AUC_{tau} from cSSSI and CABP PK patients were lower than observed AUC_{inf} by non-compartmental analysis from Phase 1 renal impairment studies of single IV doses. Differences between observed versus simulated data by the Sponsor and the Pharmacometrics Reviewer, and differences between observed data from Phase 1 renal impairment studies versus Phase 2/3 cSSSI and CABP IV trials may be partly contributed by inter-study differences and differences in subject demographics as evidenced by comparative box plots of ceftaroline CL in **Figure 2.3.2.5-11**. Compounded by these differences, the Sponsor's Monte Carlo simulation significantly under-predicts ceftaroline AUC_{tau} relative to observed AUC_{inf} from Phase 1 renal impairment studies.

Table 2.3.2.5-3 Median ceftaroline exposure (observed and simulated) for recommended dosing regimens of ceftaroline fosamil by the Reviewer (in bold and italicized font) according to renal function

Renal Function	CrCL (mL/min)	Dosing Regimen[a]	Ceftaroline AUC_{tau} (µg*h/mL)				
			Observed		Simulated		
			Phase 1 -02, -04, -18	**Phase 2/3** -03, -06, -07, -08, -09	**Phase 1** -02, -04, -18	**All**	**Phase 1/3** -04, -08, -09
			NCA	**Pop PK**	**TCA** (Reviewer)	**MCS** (Sponsor)	**Pop PK** (PM Reviewer)
Normal	>80	***600 mg Q12h***	74.9[b] (n=6)	54.9 (n=140)	72.1 (n=17)	47.7 (n=2000)	52.1 (n=797)
Mild	>50 to ≤80	***600 mg Q12h***	92.7[b] (n=6)	75.0 (n=62)	–	58.5 (n=2000)	68.6 (n=792)
Moderate	>30 to ≤50	***400 mg Q12h***	–	69.6 (n=17)	75.3 (n=6)	41.1 (n=2000)	50.3 (n=304)
Severe	≤30	400 mg Q12h	113.6[b] (n=6)	–	107.9 (n=6)	53.0 (n=2000)	58.9 (n=107)
		300 mg Q12h	–	–	81.0 (n=6)	36.4 (n=2000)	40.9 (n=107)
ESRD	(on HD)	***200 mg Q12h***	–	–	64.9 (n=6)	–	–

MCS; Monte Carlo simulation; NCA, non-compartmental analysis; Pop PK, population pharmacokinetic analysis/simulation; TCA, two-compartmental analysis

[a] All simulated doses were as 1-h IV infusions

[b] Phase 1 subjects received single doses of ceftaroline fosamil; values represent AUC_{inf} rather than AUC_{tau}

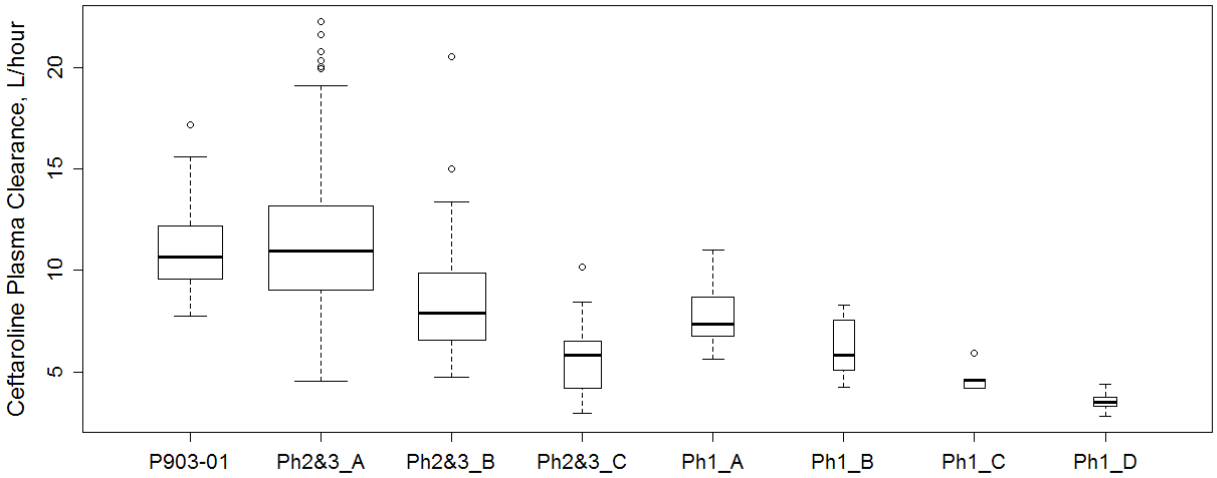
Note1: Created using Module 5.3.3, Study P903-02, Pharmacokinetic Report, Appendix 7.2

Note2: Created using Module 5.3.3, Study P903-04, Tables 14.1-8 & 14.1-9

Note3: Created using Module 5.3.3, Study P903-18, Tables 14.2-17 & 14.2-18

Note4: Created using Module 5.3.4, ICPD 00174-8 or 00174-9, Tables 4-1 & 4-2

Figure 2.3.2.5-11 Ceftaroline CL box plots across Phase 1 (P903-01 and renal impairment studies) and Phase 2/3 IV studies for subjects with normal renal function (A) or mild (B), moderate (C), or severe (D) renal impairment (estimated by population PK)



As such, renal dose recommendations should be determined rather upon data from Phase 1 renal impairment studies, which were simulated by the Reviewer using two-compartmental analysis. This is supported by comparable exposures confirmed in Phase 2/3 IV patients with moderate renal impairment versus those with normal renal function at the renal-adjusted regimen endorsed by Phase 1 data. Moreover, the downward trend in ceftaroline CL with renal impairment in patients from Phase 2/3 IV trials appears to parallel subjects from Phase 1 renal impairment studies, further validating the use of these Phase 1 data for determination of renal dosing.

2.3.2.6 Hepatic impairment

The effect of hepatic impairment has not been studied for ceftaroline fosamil.

2.3.2.7 What pregnancy and lactation use information is there in the application?

No studies with ceftaroline fosamil have been performed in pregnant or lactating females. Information on pregnancy is limited to non-clinical data and is proposed by the Sponsor for Pregnancy Category B. The excretion of ceftaroline in human milk by lactating mothers has not been assessed, and accordingly, the Sponsor recommends caution when ceftaroline fosamil is administered to nursing women.

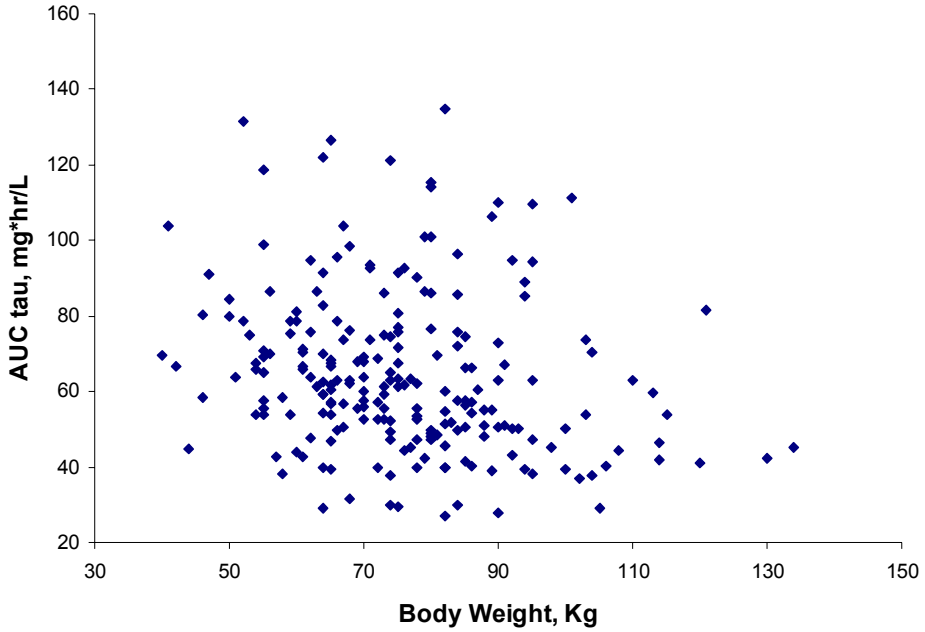
Refer to the Pharmacology/Toxicology review (A Ellis, PhD) for complete analysis of ceftaroline toxicology.

2.3.2.8 Obesity

The effect of weight on ceftaroline exposure was investigated in population PK analyses. As shown in **Figure 2.3.2.8-1**, no discernable trend was observed between body weight and

ceftaroline AUC_{tau} in cSSSI and CABP PK populations. (See Pharmacometrics Review under **Section 4, Appendices**.)

Figure 2.3.2.8-1 Ceftaroline AUC_{tau} scatter plots by body weight in pooled cSSSI and CABP PK populations (n=219)



2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Specific Phase 1 studies investigating the impact of extrinsic factors have not been conducted for ceftaroline fosamil. Potential *in vivo* drug-drug interactions were screened for with an exploratory population PK analysis of Phase 2/3 cSSSI and CABP trials (**ICPD 00174-5**).

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

In vitro metabolism, inhibition, and induction experiments suggest the potential for *in vivo* drug-drug interactions with ceftaroline fosamil is low.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

In vitro oxidative metabolism studies with human liver microsomes indicate ceftaroline fosamil and ceftaroline are not significant substrates of CYP450 isoenzymes. Little biotransformation of

ceftaroline fosamil and ceftaroline was observed in liver microsomes, with low elimination rates ranging from <0.1 to 1.0 pmol/mg protein/min (**TAK-599/00067**). Ceftaroline also showed low metabolic turnover (<12%), with 88.8-101.0% of the compound remaining in pooled human liver microsomes (**P0903-P-002**).

Genetic information regarding the metabolism of ceftaroline was not provided by the Sponsor.

2.4.2.3 Is the drug an inhibitor and/or inducer of CYP enzymes?

In vitro inhibition and induction studies indicate ceftaroline is not an inhibitor or inducer of major CYP450 isoenzymes. Minimal inhibitory effect (<20%) was exhibited by ceftaroline fosamil and ceftaroline in specific CYP450 complementary-DNA-expressing human B-lymphoblastoid-derived microsomes for 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 (**TAK-599/00067**). Ceftaroline fosamil, ceftaroline, and ceftaroline M-1 also had minor or no induction effect (<25%) on 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4/5 at clinically relevant concentrations in fresh primary cultures of human hepatocytes (**CEF-PK-01**).

2.4.2.4 Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?

In vitro P-glycoprotein (P-gp) experiments have not been conducted for ceftaroline fosamil.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No other *in vitro* metabolic/transporter experiments have been conducted for ceftaroline fosamil.

2.4.2.6 Does the label specify co-administration of another drug, and if so, has the interaction potential between these drugs been evaluated?

Co-administration of another drug is not specified in the draft label.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Target patient populations of cSSSI and CABP range from otherwise healthy patients to patients with significant co-morbidities. Ceftaroline fosamil may be used with a wide variety of co-medications from different drug classes for many different therapeutic indications.

2.4.2.8 Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Exploratory population PK analysis of Phase 2/3 cSSSI and CABP patients (n=220) indicate no clinically significant differences in ceftaroline C_{max} or AUC_{tau} with concomitant medication use (**ICPD 00174-5**). Studied concomitant medication categories were inhibitors, inducers, or substrates of major CYP450 isoenzymes; anionic or cationic drugs known to undergo active renal secretion; and vasodilator or vasoconstrictor drugs that may alter renal blood flow.

Concomitant use of CYP1A2 inhibitors (p=0.018), CYP3A4/57 inhibitors (p=0.005), renal anions (p≤0.001), and vasodilators (p≤0.001) resulted in statistically significantly higher AUC_{tau} by 19.0%, 20.3%, 17.6%, and 16.6%, respectively, than patients not using a drug in these categories. Differences in patient characteristics (e.g., age, gender, and CrCL) could account for, in part, the magnitude of differences in ceftaroline AUC_{tau} by concomitant medication use. Regardless, greater ceftaroline exposures with specified concomitant medication classes would not warrant dose adjustment and were not considered clinically significant.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Antimicrobials are routinely tested for potential synergy in combination with other agents. Combinations of ceftaroline and various antibiotics were tested against Gram-positive and Gram-negative organisms with *in vitro* checkerboard testing, where synergy was defined as inhibition of organism growth by combinations at concentrations significantly below the MIC of either agent alone (i.e., fractional inhibitory concentration indices [FICI] ≤0.50) (**P0903-M-020**). *In vitro* synergy was demonstrated with meropenem against community-acquired MRSA (n=1) and *K. pneumoniae* (n=1) and with amikacin against ESBL-producing *E. coli* (n=1) and *P. aeruginosa* (n=1).

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no significant unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding for ceftaroline fosamil.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Recommendations for renal-adjusted dosing by the Reviewer are different from those proposed by the Sponsor (see **Section 2.3.2.5** for details). There are no other unresolved issues related to dose, dosing regimens, or administration that represent significant omissions to this application.

2.5 General Biopharmaceutics

This section is not applicable as ceftaroline fosamil is formulated for IV administration.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma, urine, and dialysate fluid were quantified by four validated LC-MS/MS assays, referred to as Methods 1-4. For metabolite profiling in the mass balance study (**P903-13**), a non-validated radiometric HPLC assay (Method 6) was used for semi-quantification of metabolites in plasma, urine, and feces.

2.6.2 Which metabolites have been selected for analysis and why?

In addition to ceftaroline fosamil (prodrug), ceftaroline (active metabolite of the prodrug) and ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline) were measured in plasma, urine, and dialysate fluid. Ceftaroline is the microbiologically active entity and represents the majority of circulating and recovered moieties, followed by ceftaroline M-1.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total drug concentrations of ceftaroline were measured in all clinical studies. Plasma protein binding of ceftaroline was assessed separately with *in vitro* ultrafiltration experiments and was accounted for when assessing free (i.e., microbiologically active) exposures.

2.6.4 What bioanalytical methods are used to assess concentrations?

Four validated LC-MS/MS assays (Methods 1-4) were used for quantitation of ceftaroline fosamil, ceftaroline, and ceftaroline M-1. See **Table 2.6.4-1** for details.

Table 2.6.4-1 Summary of analytical methods for quantification of ceftaroline fosamil, ceftaroline, and ceftaroline M-1

	Method 1	**Method 2**	**Method 3**	**Method 4**
Analytical Reports (PRD-RPT-BDM)	-00128 -00131	-00127 -00129	-00077 -00299	-00080 -00300
Studies				
Phase 1	P903-01 P903-02	P903-01 P903-02	P903-04 P903-15 P903-05 P903-17 P903-11 P903-18 P903-13 P903-20 P903-14	P903-04 P903-18 P903-11 P903-20 P903-13 P903-15 P903-17
Phase 2/3	P903-03		P903-06 P903-07 P903-08 P903-09 P903-19	
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Matrix	Plasma	Urine	Plasma	Urine Dialysate fluid
Analytes	Ceftaroline fosamil Ceftaroline Ceftaroline M-1	Ceftaroline fosamil Ceftaroline Ceftaroline M-1	Ceftaroline fosamil Ceftaroline Ceftaroline M-1	Ceftaroline fosamil Ceftaroline Ceftaroline M-1
Linearity	≥0.9987	≥0.9995	≥0.9943	≥0.9926
Standard Curve	0.01-2 µg/mL	0.2-100 µg/mL	0.05-10 µg/mL 0.05-20 µg/mL	0.5-5 µg/mL 0.5-50 µg/mL
LLOQ	0.01 µg/mL	0.2 µg/mL	0.05 µg/mL	0.5 µg/mL
ULOQ	2 µg/mL	100 µg/mL	10 µg/mL 20 µg/mL	5 µg/mL 50 µg/mL
QC Samples	0.03, 0.16, 1.6 µg/mL	0.6, 8, 80 µg/mL	0.15, 2, 4, 8 µg/mL 0.15, 2, 8, 16 µg/mL	1.5, 2, 3.8 µg/mL 1.5, 15, 38 µg/mL
Accuracy				
Intra-day	Within ±8.4%	Within ±4.8%	Within ±6.2%	Within ±10.8%
Inter-day	Within ±8.7%	Within ±3.0%	Within ±4.3%	Within ±6.5%
Precision				
Intra-day	≤6.1 %CV	≤4.3 %CV	≤6.8 %CV	≤8.7 %CV
Inter-day	≤5.9 %CV	≤4.4 %CV	≤6.5 %CV	≤6.8 %CV
Stability				
Freeze-thaw	3 cycles	3 cycles	4 cycles	5 cycles
At -70 ºC	371 days	520 days	526 days	469 days
At -4 or -5 ºC	76 hours	60 hours	105 hours	48 hours
On wet ice	6 hours	22.5 hours	4 hours	4 hours

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See **Table 2.6.4-1**. When concentrations exceeded the standard curve range, samples were diluted, then assayed. Dilution integrity was verified within each clinical pharmacology study when samples dilutions were performed.

For Methods 1 and 2, a power equation ($y = Ax^b$, where x is the concentration and y is the peak height ratio) was applied for all standard curves. For Methods 3 and 4, a linear regression ($y = mx + b$, where x is the concentration and y is the peak height ratio) was applied for all standard curves with a weighting factor of 1/concentration^2 ($1/x^2$).

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See **Table 2.6.4-1**.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Accuracy was expressed as percent deviation of the concentration from its nominal concentration, and precision as %CV. See **Table 2.6.4-1**.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

See **Table 2.6.4-1**.

2.6.4.5 What is the QC sample plan?

See **Table 2.6.4-1**.

3. DETAILED LABELING RECOMMENDATIONS

Sponsor's draft label version: 30 Dec 2009

The following proposed package insert has been marked by revisions made by the Reviewer, indicated with ~~red strikethrough font~~ for deleted text and underlined blue font for inserted text. Affected sections include **Highlights**, **Dosage and Administration (2)**, **Drug Interactions (7)**, **Use in Specific Populations (8)**, and **Clinical Pharmacology (12)**.

22 pages of draft labeling withheld in full immediately following this page as B4 (CCI/TS)

4. APPENDICES

4.1 Individual Study Report Reviews

4.1.1 *In Vitro* Studies

APPEARS THIS WAY ON ORIGINAL

STUDY NO.: TAK-599/00069
REPORT NO.: PRD-RPT-BDM-00133

Pharmacokinetics of TAK-599 after intravenous injection in animals

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Laboratory Site: Pharmaceutical Research Division, Takeda Chemical Industries, Ltd.

STUDY DESCRIPTION: This study evaluated the distribution, metabolism, and excretion of ^{14}C-labeled TAK-599 following single and multiple (QD for 14 days) doses of 10 mg/kg IV in mice, rats, and monkeys. Another portion of this study used human biomaterials and investigated the erythrocytes distribution and plasma protein binding of [^{14}C]M-I *in vitro* in humans.

METHODS

Distribution into Erythrocytes: [^{14}C]M-I was added *in vitro* to the blood of mice, rats, monkeys, and humans at final concentrations of 0.5, 5, and 50 µg/mL. After incubation for 30 minutes at 37 ºC, concentrations of [^{14}C] in whole blood and plasma (obtained by centrifugation of whole blood at 3000 rpm for 15 minutes) were determined to calculate the percentage of the compound distributed in erythrocytes by using the hematocrit value.

Reviewer Comment: Source of whole blood from humans (fresh versus frozen) was not identified.

Binding to Plasma Protein: [^{14}C]M-I was added *in vitro* to the plasma of rats, mice, monkeys, and humans at final concentrations of 0.5, 5, and 50 µg/mL, and protein binding was determined by ultrafiltration using Centrifree Micropartition System™ (centrifuged at 3500 rpm for 15 minutes). Human serum albumin (HSA) and human α1-acid glycoprotein (AGP) were purchased from (b) (4)

Analytical Methods: Measurement of radioactivity ([^{14}C]) was determined by liquid scintillation counter (LSC-5100), and concentrations of total [^{14}C] and TAK-599 metabolites were expressed as TAK-599 free base equivalent value. Measurement of [^{14}C]TAK-599, [^{14}C]M-I, and metabolites were quantified by HPLC.

Reviewer Comment: Performance of analytical methods was not provided.

RESULTS

Distribution into Erythrocytes: During the incubation period, part of M-I was found to decompose, therefore the definitive distribution of M-I itself could not be determined. Rather, distribution into erythrocytes was estimated as M-I and its decomposed derivative. At 0.5-50 µg/mL, radioactivity was minimally distributed into erythrocytes of mice (0.6-3.3%), rats (0.7-1.8%), monkeys (1.6-5.0%), and humans (0%).

Binding to Plasma Protein: During the incubation period, part of M-I was found to decompose, therefore the definitive binding ratio of M-I itself could not be determined. Rather, the binding ratio to plasma protein was estimated as M-I and its decomposed derivatives. At 0.5-50 µg/mL, low percentages of plasma protein binding of [^{14}C]M-I were found in mice (32.1-35.6%), rats (36.8-40.7%), monkeys (14.2-20.0%), and humans (23.4-26.4%).

SPONSOR'S CONCLUSIONS: [^{14}C]M-I was hardly distributed in the erythrocytes, and binding to plasma proteins in mice, rats, monkeys, and humans was low at concentrations of 0.5-50 µg/mL.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

(b) (4)

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STUDY NO.: P-0903-P-001
REPORT NO.: PRD-RPT-BDM-00140

Plasma protein binding by ultrafiltration in 4 species

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Laboratory Site: [redacted] (b) (4)

STUDY DESCRIPTION: This study investigated the binding of PPI-0903M to mouse, rabbit, monkey, and human plasma proteins using ultrafiltration at concentrations of 5, 50, and 150 µg/mL.

METHODS

Non-Specific Binding: Protein-free filtrate (PFF) was prepared from plasma by centrifuging plasma in individual 30,000 molecular weight cut-off filter devices at approximately 3300 rpm. The PFF was then fortified with PPI-0903M such that the final concentration was 50 µg/mL. The spiked PFF was incubated for 20 minutes at 37 ºC, then transferred into Centrifree® ultrafiltration units and centrifuged at 3300 rpm for 20 minutes at 37 ºC. Samples of the generated ultrafiltrate were removed, mixed with methanol, and centrifuged to remove precipitated protein immediately after collection. The final supernatant was used for analysis.

Plasma Protein Binding: Testing for plasma protein binding was performed in duplicate. Plasma was fortified with PPI-0903M such that final concentrations were 5, 50, 150 µg/mL. The spiked plasma was incubated for 20 minutes at 37 ºC, then transferred into Centrifree® ultrafiltration units and centrifuged (centrifugation parameters not provided). Samples of the generated ultrafiltrate were removed, diluted with blank plasma, mixed with [redacted] (b) (4) as the internal standard, and centrifuged to remove precipitated protein immediately after collection. The final supernatant was used for analysis. Plasma samples from all species were purchased from [redacted] (b) (4) and pooled for use.

Percent protein binding was calculated as follows:

% free fraction	=	(drug concentration in ultrafiltrate / drug concentration in unfiltered spiked plasma) × 100
% bound	=	100 – % free fraction

Analytical Methods: Non-specific binding and plasma protein binding samples were analyzed with LC/MS. The targeted % recovery (= plasma post-incubation concentration / plasma pre-incubation concentration × 100) was >90%; the study was repeated if recovery was ≤85%. Mean recovery in PFF from plasma of all evaluated species was 94-102%. Mean recovery in mouse, rabbit, monkey, and human was 89-101%, 87-109%, 98-105%, and 95-107%, respectively.

RESULTS

Non-Specific Binding: Not provided. However, non-specific binding results are incorporated in the calculation of % free fraction.

Plasma Protein Binding: See **Table 1**.

Table 1. Mean (of duplicate) protein binding of PPI-0903M in mouse, rabbit, monkey, and human plasma

Species	PPI-0903M (µg/mL)	% Bound	% Free Fraction
Mouse	5	37.5%	62.5%
	50	35.8%	64.2%
	150	34.5%	65.5%
Rabbit	5	17.0%	83.0%
	50	5.5%	94.5%
	150	4.6%	95.4%
Monkey	5	16.8%	83.2%
	50	16.8%	83.2%
	150	22.2%	77.8%
Human	5	19.3%	80.7%
	50	0.9%	99.1%
	150	7.4%	92.6%

SPONSOR'S CONCLUSIONS:

- PPI-0903 has low plasma protein binding across all evaluated species.
- The highest level of plasma protein binding was observed in mouse (34.5-37.5%), and the lowest in human (0.9-19.3%) and rabbit (4.6-17.0%).
- Percent bound decreased with increasing concentration in human and rabbit plasma.
- More drug concentrations should be evaluated and in triplicate for more accurate human plasma protein binding.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

STUDY NO.: P0903-P-003
REPORT NO.: PRD-RPT-BDM-00137

Plasma protein binding by ultrafiltration in human plasma for PPI-0903M

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Laboratory Site: [redacted] (b) (4)

STUDY DESCRIPTION: This study investigated the binding of PPI-0903M to plasma proteins from human plasma using ultrafiltration at concentrations of 1, 5, 20, and 50 µg/mL.

METHODS

Plasma Protein Binding: Testing for plasma protein binding was performed in triplicate. Plasma was fortified with PPI-0903M such that final concentrations were 1, 5, 20, and 50 µg/mL. The spiked plasma was then incubated for 20 minutes at 37 ºC, then transferred into Centrifree® ultrafiltration units (centrifugation parameters not provided). Samples of the generated ultrafiltrate were removed, diluted with blank plasma, mixed with [redacted] (b) (4) as the internal standard, and centrifuged to remove precipitated protein immediately after collection. The final supernatant was used for analysis. Plasma samples from human donors were purchased from [redacted] (b) (4) and pooled for use.

Percent protein binding was calculated as follows:

% free fraction	=	(drug concentration in ultrafiltrate / drug concentration in unfiltered spiked plasma) × 100
% bound	=	100 – % free fraction

Reviewer Comment: Although not described within the study report, it appears non-specific binding was performed and incorporated into the calculation of % free fraction.

Analytical Methods: Plasma protein binding samples were analyzed with LC/MS. The targeted % recovery (= plasma post-incubation concentration / plasma pre-incubation concentration × 100) was >90%; the study was repeated if recovery was ≤85%. Overall, % recovery were >90% across all concentrations.

RESULTS

Plasma Protein Binding: See **Table 1**.

Table 1. Mean (of triplicate) protein binding of PPI-0903M in human plasma

PPI-0903M (µg/mL)	% Bound	% Free Fraction
1	28.0%	72.0%
5	21.3%	78.7%
20	14.5%	85.8%
50	15.9%	84.1%

SPONSOR'S CONCLUSIONS:

- PPI-0903M plasma protein binding was 14.5-28.0% in human plasma at 1-50 μg/mL.
- Percent bound decreased with increasing concentrations, with similar values observed at 20 and 50 μg/mL.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results. Results from this study will be used for the product label as evaluated concentrations more appropriately cover the clinically relevant range and testing was more accurately performed in triplicate than Study P-0903-P-001.

STUDY NO.: PF04315
REPORT NO.: MC04315

Determination of the potential metabolites of PPI-0903 formed in human plasma

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Laboratory Site: (b) (4)

STUDY DESCRIPTION: This study 1) investigated the stability of PPI-0903 in human plasma and in plasma treated with a phosphatase inhibitor, and 2) determined the molecular masses of any potential metabolites of PPI-0903 formed in human plasma during *in vitro* incubations.

METHODS

Study Procedures: PPI-0903 was incubated with human plasma, stabilized (i.e., with phosphatase inhibitor) human plasma, and 50 mM phosphate buffer at a final concentration of 1 µM (or 0.68 µg/mL). Samples were obtained at 0 (pre-incubation), 1, 2, and 4 hours of incubation at 37 ºC by freezing samples prior to extraction in order to terminate enzyme activity. Testing was performed in triplicate, and blank human plasma with sodium heparin was acquired from (b) (4) and pooled for use.

Potential metabolites were identified by MS scanning, where the appearance of potential metabolites (and disappearance of PPI-0903) over time was measured by comparing peak heights at each time point to peak heights at 0 hour. By product ion scanning, the spectra of potential metabolites were compared to the spectrum of PPI-0903 to determine molecular similarity.

Analytical Methods: Incubation samples were analyzed by LC/MS/MS in two parts: 1) MS scanning for potential metabolites and 2) product ion scanning of potential metabolites.

MS scans of 100-850 amu were performed in search of peaks present in the 1-hour sample but not in the 0-hour sample. Remaining time points were then searched for the presence of peaks found in the 1-hour sample. Peaks exhibiting a height that trended up or up then down with time were considered to be potential metabolites.

Product ion scans of 50-720 amu were performed on the 0-hour sample to obtain the spectrum of PPI-0903 and for each potential metabolite by using the time point for which the highest concentration was observed in the MS scan. Spectra of potential metabolites were compared to the spectrum of PPI-0903 to determine the degree of structural similarity between potential metabolites and PPI-0903.

Reviewer Comment: Performance of analytical methods was not provided.

RESULTS

Metabolic Stability: See **Table 1**. In human plasma at 37 ºC, PPI-0903 at an initial concentration of 1 µM was consumed to near completion by 2 hours, and the half-life was estimated to be 19 minutes. In stabilized (i.e., with phosphatase inhibitor) human plasma, consumption of PPI-0903 was greatly reduced and also appeared stable in buffer, although data were variable in both mediums, preventing estimation of half-life. Formation of putative metabolites was also considerably lower in stabilized plasma and buffer than in plasma.

Table 1. Degradation of PPI-0903 and formation of putative metabolites (M1-M4)

Sample	PPI-0903 peak height *m/z* 684.75 6.5 min	M1 peak height *m/z* 208 6.0 min	M2 peak height *m/z* 561 6.0 min	M3 peak height *m/z* 605 5.99 min	M4 peak height *m/z* 623 5.5 min
Plasma					
Blank	29,070	7,748	15,263	51,209	1,578
0 h	3,321,642	148,950	72,038	2,421,134	7,760
1 h	409,644	1,620,371	725,259	11,028,940	232,105
2 h	42,044	371,740	236,874	3,246,885	290,425
4 h	26,028	45,567	12,264	249,381	222,174
Stabilized Plasma					
Blank	8,733	8,962	0	28,854	3,221
0 h	3,134,619	10,184	2,421	226,688	4,794
1 h	5,174,170	16,191	21,853	478,513	11,081
2 h	3,378,994	60,991	0	484,606	22,279
4 h	1,266,091	29,709	0	175,058	56,593
Buffer					
Blank	10,540	10,791	7,432	30,332	1,318
0 h	924,420	37,276	1,902	214,346	1,692
1 h	1,747,942	35,094	3,981	289,608	5,830
2 h	1,985,124	42,570	0	217,211	5,461
4 h	1,145,950	38,115	0	266,560	2,774

Reviewer Comment: The Sponsor indicates the reason for data variability is likely due to the full scan method, and that tests have shown data collected in MRM mode with identical chromatographic conditions were more reproducible than the full scan mode (data not provided). Reasons for higher variability in full scan mode were listed as: the collection of fewer points per peak, greater susceptibility to matrix interference, and higher background because of less selectivity. However, the Sponsor maintains data variability of the full scan mode does not alter the conclusions of the qualitative study.

PPI-0903 (Parent): PPI-0903 displayed a characteristic ionized mass of *m/z* 685, while showing an intense product ion at *m/z* 208. The product ion spectrum also contained fragments at *m/z* 118 and 262.

Putative Metabolites: Four ions of significance were found.

- **M1 (*m/z* 208, 6.0 min retention time):** M1 appears to be an in-source fragment of M3. Attempts to collect a product ion spectrum for M1 were unsuccessful. However, the Sponsor indicates the product mass of M1 is consistent with two *m/z* 209 fragments (joined together by disulfide linkage with a loss of a hydrogen molecular), which were produced by degradation of M3 in the mass spectrometer source by cleavage of the thioether function.

- **M2 (*m/z* 561, 6.0 min retention time):** M2 appears to be an in-source fragment of M3, by neutral loss of a carbon dioxide molecule from M3.
- **M3 (*m/z* 605, 5.99 min retention time):** M3 appears to be PPI-0903M; the mass of M3 corresponds with the loss of phosphate group on PPI-0903.
- **M4 (*m/z* 623, 5.5 min retention time):** M4 appears to be PPI-0903M-1; the mass of M4 corresponds with the loss of phosphate group followed by hydrolysis of the β-lactam ring.

SPONSOR'S CONCLUSIONS:
- PPI-0903 is consumed quickly in the presence of human plasma (half-life, 19 min).
- The metabolism of PPI-0903 in human plasma appears to be mediated by a phosphatase enzyme.
- Four ions of significance were observed, two of which were identified as potential metabolites: M3, the major metabolite, followed by M4.
- M3 was the protonated molecular ion of PPI-0903M, a known phosphorylated metabolite of PPI-0903.
- M4 was the protonated molecular ion of PPI-0903M-1, produced from hydrolysis of the β-lactam ring of PPI-0903M.
- M1 and M2 were in-source mass spectrometry fragments of M3.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

STUDY NO.: TAK-599/00067
REPORT NO.: PRD-RPT-BDM-00139

In vitro metabolism of TAK-599 and M-I by cytochrome P450

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Laboratory Site: Pharmaceutical Research Division, Takeda Chemical Industries, Ltd.

STUDY DESCRIPTION: This study investigated 1) the *in vitro* oxidative metabolism of TAK-599 and M-I, and 2) the inhibitory effects of TAK-599 and M-I on CYP450-specific activities.

METHODS
Study Procedures: Human hepatic microsomes were obtained form (b) (4) Specific CYP cDNA-expressing 1A1, 1A2, 2A6, 2B6, 2C8, 2C9(Arg), 2C9(Cys), 2C19, 2D6, 2E1, and 3A4 human B-lymphoblastoid-derived microsomes and control human B-lymphoblastoid-derived microsomes were purchased from (b) (4) .

For oxidative metabolism, mixtures of 1 mg/mL microsomal protein in 50 mM KH_2PO_4 - K_2HPO_4 phosphate buffer (pH 7.4) containing an NADPH-generating system were incubated (in duplicate) for 1 hour at 37 ºC with a final concentration of 10 µM for [^{14}C]TAK-599 (or 6.8 µg/mL) and [^{14}C]M-I (or 6.0 µg/mL).

For CYP450 inhibition, mixtures of microsomes derived from specific CYP cDNA-expressed human B-lymphoblastoid cells in 50 mM KH_2PO_4 - K_2HPO_4 phosphate buffer (pH 7.4) containing an NADPH-generating system were incubated (in duplicate) with final concentrations of 1, 10, and 100 µM for TAK-599 (or up to 68.5 µg/mL) and M-I (or up to 60.5 µg/mL). For 2A6, 2B6, and 2C9 microsomes, 50 mM Tris-HCl buffer (pH 7.4) was used instead of the phosphate buffer. Pre-incubation was initiated with the addition of the NADPH-generating system for 5 minutes at 37 ºC, prior to the addition of microsomes. Specific marker enzymatic activities of the following CYP450 isoforms were assayed by published methods with slight modifications. Control marker enzyme activities were measured for pre-incubation samples in the presence of saline containing 3% sodium bicarbonate (w/v) alone without TAK-599 or M-I.

1A1, 1A2	7-ethoxyresorufin *O*-deethylation
2A6	coumarin 7-hydroxylation
2B6	ethoxycoumarin *O*-deethylation
2C8, 2C9(Arg), 2C9(Cys)	tolbutamide hydroxylation
2C19	S-(+)-mephenytoin 4'-hydroxylation
2D6	(±)-bufuralol 1'-hydroxylation
2E1	4-nitrophenol hydroxylation
3A4	testosterone 6β-hydroxylation

Reviewer Comment: Probe CYP450 substrates are those recognized by the FDA (as of 2006) for in vitro investigation except those used for 2C8 and 2E1.

Analytical Methods: [^{14}C]TAK-599, [^{14}C]M-I, and metabolites in incubation mixtures were analyzed by HPLC. Radioactivity was measured by a liquid scintillation counter.

Reviewer Comment: Performance of analytical methods was not provided.

RESULTS

Oxidative Metabolism: See **Table 1**. Both TAK-599 and M-I were hardly metabolized, and there were no metabolites specifically formed by human hepatic microsomes compared to non-clinical species.

Table 1. Mean (of duplicate) values for *in vitro* metabolism of [^{14}C]TAK-599 and [^{14}C]M-I in hepatic microsomes

Species	Incubation with [^{14}C]TAK-599		Incubation with [^{14}C]M-I		
	TAK-599 Elimination Rate (pmol/mg protein/min)	M-I Formation Rate (pmol/mg protein/min)	M-I Elimination Rate (pmol/mg protein/min)	Metabolite1 of M-I Formation Rate (pmol/mg protein/min)	Metabolite2 of M-I Formation Rate (pmol/mg protein/min)
Mouse	<0.1	<0.1	<0.1	<0.1	0.1
Rat (male)	<0.1	<0.1	1.0	0.3	<0.1
Rat (female)	<0.1	<0.1	0.2	<0.1	<0.1
Dog	<0.1	<0.1	<0.1	<0.1	0.2
Monkey	<0.5	0.1	0.4	0.3	<0.1
Human	<0.1	<0.1	0.7	0.4	<0.1

Reviewer Comment: Conversion of TAK-599 to M-I and M-I to unknown metabolites (Metabolite1 and Metabolite2 of M-I) do not appear to be mediated by CYP450 enzymes. TAK-599 is thought to convert to M-I via phosphatase enzyme and at least one of the metabolites of M-I are produced by hydrolysis of the β-lactam ring of M-I.

CYP450 Inhibition: See **Figure 1** and **Figure 2**. TAK-599 and M-I showed little inhibitory effect (<20%) on CYP450 isoform-specific metabolic activities even at 100 μM.

Reviewer Comment: The Sponsor investigated the inhibitory effects of TAK-599 and M-I on the appropriate CYP450 isoforms. Clinical drug interactions via CYP inhibition are not anticipated with TAK-599 or M-I, as the highest tested concentration of 100 μM (or ~60-70 μg/mL) exceeds clinical concentrations anticipated for both compounds at the proposed therapeutic dose.

SPONSOR'S CONCLUSIONS:

- TAK-599 and M-I were hardly metabolized by hepatic microsomes from mice, rats, dogs, monkeys, and humans, and there was no metabolite specific to humans.
- TAK-599 and M-I would not alter CYP-mediated metabolism of concomitantly administered drugs.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

Figure 1. Mean (of duplicate) inhibitory effects of **TAK-599** on marker enzyme activities with specific human CYP-expressing microsomes

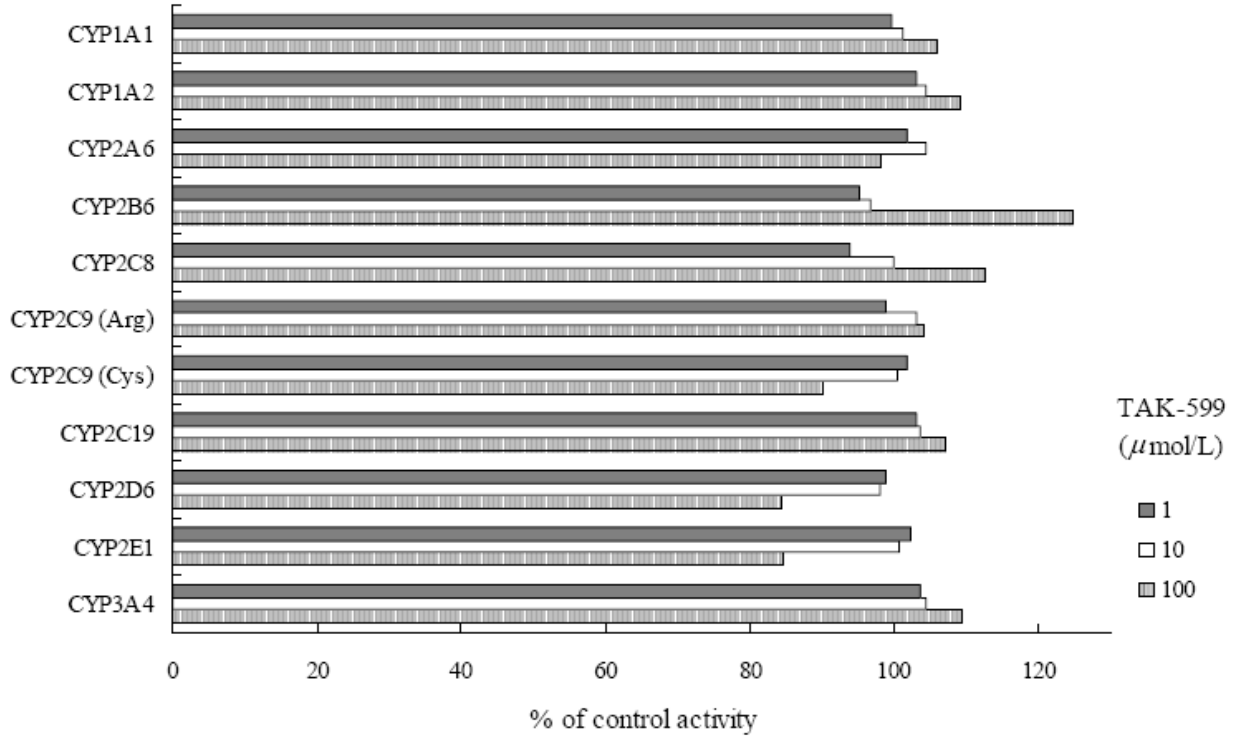
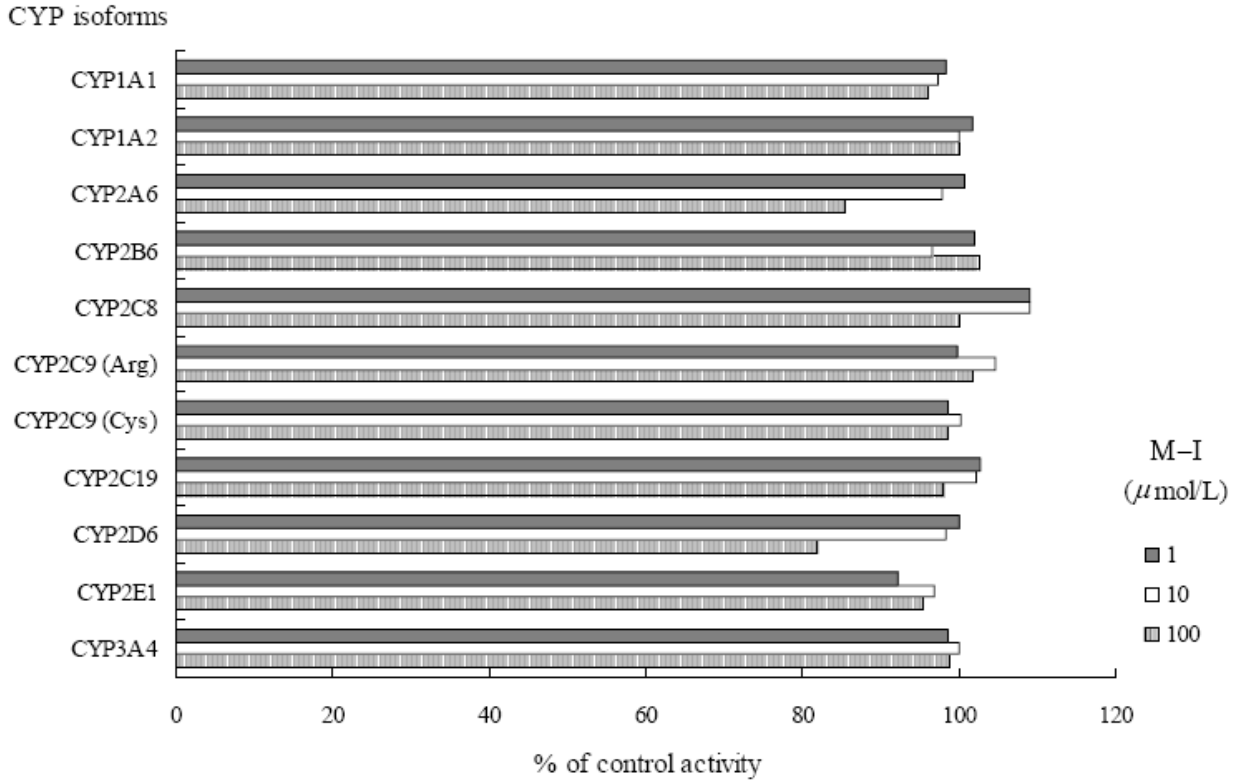


Figure 2. Mean (of duplicate) inhibitory effects of **M-I** on marker enzyme activities with specific human CYP-expressing microsomes



STUDY NO.: P0903-P-002
REPORT NO.: PRD-RPT-BDM-00142

In vitro metabolic stability

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Laboratory Site: [redacted] (b) (4)

STUDY DESCRIPTION: This study investigated the *in vitro* metabolic stability of PPI-0903M in human liver microsomes to address whether PPI-0903M is a major substrate of CYP450 isoenzymes.

METHODS
Study Procedures: PPI-0903M was incubated (in duplicate) at 5 and 100 µM (or up to 60.5 µg/mL) with pooled human liver microsomes for 30 minutes at ~37 ºC. Samples were obtained at 0 (pre-incubation) and 30 minutes by adding ice-cold [redacted] (b) (4) as the internal standard to terminate incubation. Negative controls used both boiled microsomes and microsomes containing no NADPH (to confirm chemical stability of PPI-0903M in the matrix) and positive controls used 7-ethoxycoumarin (to confirm metabolic stability of microsomal fractions).

Reviewer Comment: The highest tested concentration of 100 µM (or 60.5 µg/mL) exceeds clinical concentrations anticipated for PPI-0903M at the proposed therapeutic dose.

Metabolic stability was assessed by comparing the concentration of PPI-0903M at 30 versus 0 minutes, to calculate % loss of the parent compound. The % degradation was calculated in the same manner for negative and positive controls.

Analytical Methods: Samples of the incubate supernatant were analyzed by LC-MS. Conversion of the positive control, 7-ethoxycoumarin, to 7-hydroxycoumarin was measured by HPLC.

Reviewer Comment: Performance of analytical methods was not provided.

RESULTS
Metabolic Stability: See **Table 1**. PPI-0903M showed little metabolic turnover with 88.8% and 101.0% of the parent compound remaining after 30-minute incubations at 5 and 100 µM, respectively. Corresponding negative controls also showed little loss of the parent compound (confirming chemical stability of PPI-0903M under test conditions) and the positive control had significant turnover that matched historical data at the testing laboratory site (confirming satisfactory metabolic activity in microsomes).

Table 1. Mean (of duplicate) values for *in vitro* metabolism of PPI-0903M in human liver microsomes

Matrix	PPI-0903M (µM)	% Remaining
Human Microsomes	5	101.0%
	100	88.8%
Negative Control		
Boiled Microsomes	5	103.5%
	100	100.9%
Microsomes without NADPH	5	93.9%
	100	99.0%
Positive Control		
7-ethoxycoumarin	25	36.8%

SPONSOR'S CONCLUSIONS:

- In a well-established assay using pooled human liver microsomes that express all major drug-metabolizing CYP450 isoenzymes, little PPI-0903M metabolism could be detected (CYP450-mediated or otherwise) either in the presence of absence of NADPH.
- PPI-0903M is not a major substrate for human hepatic CYP450 enzymes and CYP450-dependent hepatic metabolic pathway plays little or no role in the degradation of PPI-0903M.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

STUDY NO.: CEF-PK-01

***In vitro* evaluation of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 as inducers of cytochrome P450 expression in cultured human hepatocytes**

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Laboratory Site: [redacted] (b) (4)

STUDY DESCRIPTION: This study investigated the effects of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 on the expression of CYP450 enzymes in fresh primary cultures of human hepatocytes.

METHODS

Study Procedures: Three preparations of freshly isolated and cultured hepatocytes were obtained from three separate human livers and treated once daily for three consecutive days with the following:

Ceftaroline fosamil	(Test compound)	5, 15, and 50 µM (or up to 34.2 µg/mL)
Ceftaroline	(Test compound)	50, 150, and 500 µM (or up to 302.4 µg/mL)
Ceftaroline M-1	(Test compound)	5, 15, and 50 µM (or up to 31.2 µg/mL)
Negative Control		
0.1% dimethyl sulfoxide, DMSO	(Vehicle)	
Positive Control		
Omeprazole	(Inducer of 1A2)	100 µM
Phenobarbital	(Inducer of 2B6)	750 µM
Rifampin	(Inducer of 2C8, 2C9, 2C19, and 3A4)	10 µM

Reviewer Comment: The highest tested concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 exceeds clinical concentrations anticipated of all three compounds at the proposed therapeutic dose. Probe CYP450 inducers and tested concentrations are those recognized by the FDA (as of 2006) for in vitro investigation.

Microsomes were incubated at 37 ºC in mixtures (target pH 7.4) containing high-purity water, potassium phosphate buffer, MgCl2, EDTA, an NADPH generating system, and a marker CYP450 substrate at the final concentration and incubation period indicated below.

1A2	Phenacetin	80 µM	30-min incubation
2B6	Bupropion	500 µM	30-min incubation
2C8	Amodiaquine	20 µM	10-min incubation
2C9	Diclofenac	100 µM	10-min incubation
2C19	*S*-mephenytoin	400 µM	30-min incubation
3A4/5	Testosterone	250 µM	10-min incubation

Reviewer Comment: The Sponsor investigated the inductive effects of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 on the appropriate CYP450 isoenzymes. Probe CYP450 substrates are those recognized by the FDA (as of 2006) for in vitro investigation.

Analytical Methods: The following metabolites were monitored for by validated LC/MS/MS.

1A2	Acetaminophen
2B6	Hydroxybupropion
2C8	*N*-desethylamodiaquine
2C9	4′-hydroxydiclofenac
2C19	4′-hydroxymephenytoin
3A4/5	6β-hydroxytestosterone

Reviewer Comment: Performance of analytical methods was not provided.

RESULTS

Cultured Human Hepatocytes: In general, human hepatocytes treated with vehicle, ceftaroline fosamil, ceftaroline, ceftaroline M-1, or known CYP450 inducers exhibited normal hepatocyte morphology. Cultured hepatocytes appeared free of detectable autophagic and lipid vesicles, contained intact cell membranes and granular cytoplasm with one or two centrally located nuclei, and were cuboidal.

Hepatocyte cultures treated with ceftaroline fosamil, ceftaroline, and ceftaroline M-1 for three consecutive days did not cause any detectable cytotoxicity based on release of lactate dehydrogenase (LDH).

CYP450 Induction: See **Table 1**. Treatment of all three preparations of hepatocytes with positive controls resulted in anticipated and appropriate increases in CYP450 activity. Ceftaroline fosamil, ceftaroline, and ceftaroline M-1 had little or no effect on 2C8 (amodiaquine *N*-dealkylase), 2C9 (diclofenac 4′-hydroxylase), 2C19 (*S*-mephenytoin 4′-hydroxylase), and CYP3A4/5 (testosterone 6β-hydroxylase) activity.

For 1A2 (phenacetin *O*-dealkylase), treatment of cultured human hepatocytes with up to 50 µM ceftaroline fosamil and 500 µM ceftaroline had little or no effect, while 50 µM ceftaroline M-1 caused an increase in CYP1A2 activity (up to 4.69 fold). The increase caused by ceftaroline M-1 was >20% as effective as the positive control (omeprazole) in two humans, but on average, only 19% as effective as the control.

Reviewer Comment: Ceftaroline M-1 is unlikely to cause clinically relevant drug interactions due to CYP1A2 induction, as the C_{max} for ceftaroline M-1 is approximately only 14% that of the bioactive ceftaroline at the proposed therapeutic dose. Moreover, according to the 11 Sep 2006 Draft Guidance for Drug Interaction Studies, a drug that produces a change ≥40% of the positive control is considered an in vitro enzyme inducer, and ceftaroline M-1 caused a change that was only ~20% of the positive control at the highest tested concentration of 50 µM.

For 2B6 (bupropion hydroxylase), ceftaroline fosamil and ceftaroline M-1 had little or no effect, while treatment with up to 500 µM ceftaroline caused a 32.6% decrease in activity.

Reviewer Comment: It is unclear why ceftaroline at 500 µM caused a significant decrease in CYP2B6 activity; this may be related to study methods. Regardless, ceftaroline is unlikely to cause clinically relevant drug interactions via CYP2B6, induction or otherwise.

Table 1. Mean (of triplicate) induction effects of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 on CYP450 enzyme activity in cultured human hepatocytes

Treatment	Induction Ratio (Treated/Vehicle Control)					
	1A2	2B6	2C8	2C9	2C19	CYP3A4/5
Ceftaroline fosamil						
5 µM	1.10	0.845	0.978	0.931	0.902	1.02
15 µM	1.11	1.00	1.11	0.985	1.02	1.11
50 µM	0.961	0.815	0.847	0.899	0.900	0.948
Ceftaroline						
50 µM	1.13	0.894	0.963	1.12	0.975	1.13
150 µM	1.06	0.832	0.893	0.955	0.962	0.996
500 µM	0.940	0.674	0.785	0.886	0.807	0.919
Ceftaroline M-1						
5 µM	1.27	0.923	0.942	0.990	0.934	1.08
15 µM	1.86	0.941	0.916	0.945	0.892	0.915
50 µM	4.69	1.00	1.03	0.993	0.913	1.09
Vehicle						
Dimethyl sulfoxide, 0.1%	1.00	1.00	1.00	1.00	1.00	1.00
Positive Control						
Omeprazole, 100 µM (1A2)	20.4	6.62	1.76	1.39	1.25	1.60
Phenobarbital, 750 µM (2B6)	1.92	8.28	3.57	1.80	1.94	10.9
Rifampin, 10 µM (2C8, 2C9, 2C19, and 3A4)	1.59	5.24	4.34	2.04	4.26	12.3

SPONSOR'S CONCLUSIONS:

- Under conditions where positive controls caused anticipated induction of CYP450 enzymes, treatment of primary cultures of hepatocytes with ceftaroline fosamil, ceftaroline, or ceftaroline M-1 had no effect (<25% change) on 2C8, 2C9, 2C19, and 3A4/5 activity.
- For 1A2, ceftaroline fosamil and ceftaroline had no effect (<25% change) on 1A2 activity, while treatment with 50 µM ceftaroline M-1 caused 4.69-fold increase in 1A2 activity (19% as effective as the positive control, omeprazole).
- For 2B6, treatment with up to 500 µM ceftaroline caused a 32.6% decrease in CYP2B6 activity.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

4.1.2 General Pharmacokinetics/Pharmacodynamics

APPEARS THIS WAY ON ORIGINAL

STUDY NO.: P903-01

A Phase 1, randomized, double-blind, dose escalation study to determine the safety, tolerability, and pharmacokinetics of PPI-0903 for injection in healthy subjects

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Date(s): 12 May 2004 – 13 Sep 2004
Investigator(s): AJ Williams, MD
Clinical Site(s): Matrix Drug Development, Ltd., Rhodfa Marics, Llantrisant, UK
Analytical Site(s): (b) (4)

OBJECTIVE(S):

- To determine the safety and pharmacokinetic profile of PPI-0903 when administered intravenously to healthy adult subjects for up to 14 days
- To determine the highest safe and tolerated dosing regimen of intravenously administered PPI-0903

METHODS

Study Design: P903-01 was a single-center, prospective, randomized, double-blind study of ascending single and multiple doses of PPI-0903 administered intravenously to healthy adult subjects (n=72). The study was conducted in two parts, with 8 subjects (6 active: 2 placebo) for each dosing cohort; Part 1 consisted of single doses and Part 2 of multiple doses (**Table 1**).

Table 1. Study/Dosing design of Part 1 (single-dose) and Part 2 (multiple-dose)

Part 1 (n=48)	Group 1 (101-108)	50 mg ×1 (1-hour IV infusion)
	Group 2 (201-208)	100 mg ×1 (1-hour IV infusion)
	Group 3 (301-308)	250 mg ×1 (1-hour IV infusion)
	Group 4 (401-408)	500 mg ×1 (1-hour IV infusion)
	Group 5 (501-508)	750 mg ×1 (1-hour IV infusion)
	Group 6 (601-608)	1000 mg ×1 (1-hour IV infusion)
Part 2 (n=24)	Group 1 (1001-1008)	300 mg Q12 ×14 days (1-hour IV infusions)
	Group 2 (2001-2008)	600 mg Q12 ×14 days (1-hour IV infusions)
	Group 3 (3001-3008)	800 mg Q24 ×7 days (1-hour IV infusions)

Inclusion Criteria: Males and females of non-childbearing potential; 18-62 years of age (inclusive); 50-100 kg (inclusive) in weight; 18.5-29.9 kg/m^2 (inclusive) in body mass index; and in good health as confirmed by medical history, physical exam, and laboratory evaluations were enrolled.

Treatment: For Part 1, PPI-0903 was administered as a single IV dose (50, 100, 250, 500, 750, and 1000 mg) on Day 1. For Part 2, PPI-0903 was administered as multiple IV doses on Days 1-14 (300 and 600 mg Q12) or Days 1-7 (800 mg Q24). PPI-0903 was reconstituted with 1.9% L-arginine in Water for Injection, and administered within 6 hours of reconstitution. Placebo was administered as USP 0.9% Sodium Chloride Solution. All doses were in a volume of 140 mL and administered as a 1-hour IV infusion.

Subjects were required to abstain from any medications (including over-the-counter remedies) from 7 days prior to first dose administration until after completion of follow-up. Subjects fasted from midnight on the night before each Study Day, and standardized meals, snacks, and beverages were provided during confinement. Subjects were also required to abstain from alcohol from 48 hours before Study Day 1 until after completion of follow-up and caffeine-containing foods or drinks during confinement.

Sample Collection: Plasma and urine samples were collected (**Table 2**) and analyzed for pharmacokinetic purposes.

Table 2. Pharmacokinetic sampling scheme for Part 1 (single-dose) and Part 2 (multiple-dose)

PART 1	
DAY 1	**Plasma** • Pre-dose • 20, 40, and 55 min AFTER START of infusion • 0.08, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36, and 48 h AFTER END of infusion **Urine** • 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, and 24-48 h AFTER START of infusion
PART 2	
DAY 1	**Plasma** • Pre-dose • 20, 40, and 55 min AFTER START of infusion • 0.08, 0.25, 0.5, 1, 2, 4, 8, and 12 h AFTER END of infusion **Urine** • 0-2, 2-4, 4-6, 6-8, 8-10, and 10-12 h AFTER START of infusion
DAYS 2-13 (Groups 1-2) **- OR -** **DAYS 2-6** (Group 3)	**Plasma** • Pre-dose (within 30 min BEFORE START of infusion of the first dose of the day)
DAY 14 (Groups 1-2) **- OR -** **DAY 7** (Group 3)	**Plasma** • Pre-dose (within 30 min BEFORE START of infusion) • 20, 40, and 55 min AFTER START of infusion • 0.08, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 h AFTER END of infusion **Urine** • 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, and 24-48 h AFTER START of infusion

Analytical Methods: Pharmacokinetic samples were analyzed for PPI-0903, PPI-0903M, and PPI-0903M-1 by validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) for plasma (Method 1; PRD-RPT-BDM-00128, 2004 and PRD-RPT-BDM-00131, 2007) and urine assay (Method 2; PRD-RPT-BDM-00129, 2004 and PRD-RPT-BDM-00127, 2007) (**Table 3**). All concentrations below the limit of quantification (BLQ) were excluded from pharmacokinetic analysis.

According to the Analytical Laboratory, there was a shipment of samples on 24 May 2004 (consisting of 277 plasma samples and 133 urine samples) that was received thawed. In response to FDA request for information, additional details regarding thawed samples were provided as shown in **Table 4** (submitted as SDN 014 under NDA 200-327 on 30 April 2010).

Reviewer Comment: It is unlikely that use of data supplied by these thawed samples will significantly alter study conclusions and will not impact pharmacokinetic results for the proposed therapeutic regimen of 600 mg Q12 for labeling.

Table 3. Bioanalytical results of PPI-0903, PPI-0903M, and PPI-0903M-1 in plasma and urine

Criterion	PPI-0903	PPI-0903M	PPI-0903M-1	Comments
PLASMA				
Range	0.010-2.0 µg/mL (1:10 & 1:100 dilution tested with 4.0 µg/mL)	0.010-2.0 µg/mL (1:10 & 1:100 dilution tested with 4.0 µg/mL)	0.010-2.0 µg/mL (1:10 & 1:100 dilution tested with 4.0 µg/mL)	Satisfactory
LLOQ	0.010 µg/mL	0.010 µg/mL	0.010 µg/mL	Satisfactory
Linearity	R^2 ≥0.9983	R^2 ≥0.9981	R^2 ≥0.9981	Satisfactory
Accuracy	Within ±5.4%	Within ±8.3%	Within ±1.3%	Satisfactory
Precision	≤11.1 %CV	≤9.4 %CV	≤11.3 %CV	Satisfactory
Stability	• Study Dates: 12 May 2004 – 13 Sep 2004 • Analysis Dates: 20 May 2004 – 6 Oct 2004 • Stability: 371 days at -70 ºC			Satisfactory
URINE				
Range	0.200-100.0 µg/mL (1:10 & 1:100 dilution tested with 200.0 µg/mL)	0.200-100.0 µg/mL (1:10 & 1:100 dilution tested with 200.0 µg/mL)	0.200-100.0 µg/mL (1:10 & 1:100 dilution tested with 200.0 µg/mL)	Satisfactory
LLOQ	0.200 µg/mL	0.200 µg/mL	0.200 µg/mL	Satisfactory
Linearity	R^2 ≥0.9993	R^2 ≥0.9991	R^2 ≥0.9995	Satisfactory
Accuracy	Within ±10.3%	Within ±6.2%	Within ±8.3%	Satisfactory
Precision	≤41.8 %CV	≤33.0 %CV	≤38.9 %CV	**Unsatisfactory**[a]
Stability	• Study Dates: 12 May 2004 – 13 Sep 2004 • Analysis Dates: 4 Jul 2004 – 28 Sep 2004 • Stability: 520 days at -70 ºC			Satisfactory

[a] *Analytical Laboratory indicates 1 low and 1 intermediate QC sample from different runs contained elevated concentrations of PPI-0903, PPI-0903M, PPI-0903M-1, which resulted in increased %CV*

Table 4. Pharmacokinetic samples received thawed on 24 May 2004

Thawed Samples	Action Taken
Part 1, Group 1 (single 50 mg dose)	
Duplicate/Backup – Plasma & Urine	Not analyzed/used
Part 1, Group 2 (single 100 mg dose)	
Original – Urine	Not analyzed/used • Backup samples received in good condition on 27 May 2004 were analyzed instead and reported as final results
Original – Plasma	**Analyzed and reported as final results** • Results from original samples reported along with backup samples that were received in good condition on 27 May 2004 and analyzed for re-assay only • Reported concentrations likely underestimates due to limited stability in plasma at room temperature

Pharmacokinetic Assessment: Pharmacokinetic parameters for PPI-0903, PPI-0903M, and PPI-0903M-1 were determined using single- and multiple-dose data with non-compartmental methods. Parameters included the following:

- C_{max}, peak observed plasma concentration
- AUC_{inf}, area under the curve from time 0 to infinity

- AUC_τ, area under the curve during a dosing interval
- T_{max}, corresponding time of C_{max}
- C_{min}, pre-dose trough plasma concentration
- $t_{1/2}$, elimination half-life
- CL, plasma clearance (adjusted for molecular weight for respective metabolite: PPI-0903M/PPI-0903 = 604.70/684.68 = 0.883; PPI-0903M-1/PPI-0903 = 622.72/684.68 = 0.909)
- CL_r, renal clearance
- % Urinary Recovery, percent of dose excreted in urine (adjusted for molecular weight for respective metabolite: PPI-0903M/PPI-0903 = 604.70/684.68 = 0.883; PPI-0903M-1/PPI-0903 = 622.72/684.68 = 0.909)
- V_{ss}, steady-state volume of distribution
- V_z, volume of distribution of terminal phase (adjusted for molecular weight for respective metabolite: PPI-0903M/PPI-0903 = 604.70/684.68 = 0.883; PPI-0903M-1/PPI-0903 = 622.72/684.68 = 0.909)
- Accumulation Ratio, ratio of last dose AUC_τ to first dose AUC_τ

Statistical Methods: Geometric mean and geometric coefficient of variation (geometric %CV) were computed for pertinent pharmacokinetic parameters by treatment group.

RESULTS

Study Population: In total, 72 healthy adults were enrolled; 54 of which were administered active drug (36, single dose; 18, multiple dose). All 72 subjects were male, 67/72 (93.1%) were Caucasian, mean age per treatment group ranged 21-31 years, and mean weight per treatment group ranged 78-84 kg.

Pharmacokinetics: Several protocol deviations with potential implications on pharmacokinetic results were identified (**Table 5** and **Table 6**).

Table 5. Protocol deviations for **Part 1 (single-dose)**

Part 1 (Single-dose)		
Deviation	**N**	**Comment**
Dosing		
Infusion time 61 min	1 occurrence each in 5/36 subjects	Acceptable
Sampling - Plasma		
Sampling time deviation	Many	Acceptable • Most deviated by ≤5 min; actual sample times used in pharmacokinetic analysis
Missing collection time	8 samples total from 7/36 subjects	Acceptable • Concentrations reported for 4/8 samples; scheduled times (24, 36, or 48 h) used in pharmacokinetic analysis • Results not significantly different from other subjects in the same dosing group at the same time points
Bioanalytical - Plasma		
Missing results	2 samples total from 2/18 subjects	Acceptable • Missing results not anticipated to have significant impact

Table 6. Protocol deviations for **Part 2 (multiple-dose)**

Part 2 (Multiple-dose)		
Deviation	**N**	**Comment**
Dosing		
Infusion time deviated by ≤5 min	1-4 occurrences each in 9/18 subjects	Acceptable
Infusion time 2 h 11 min	1 occurrence in 1/18 subjects	Acceptable • Did not occur with intensive pharmacokinetic sampling
Infusion time 67 min	1 occurrence in 1/18 subjects	Acceptable • Did not occur with intensive pharmacokinetic sampling
Sampling - Plasma		
Sampling time deviation	Many	Acceptable • Most deviated by ≤5 min; actual sample times used in pharmacokinetic analysis
Missing collection time	4 samples total from 3/18 subjects	Acceptable • Concentrations reported for all 4 samples; scheduled times (pre-dose) used in pharmacokinetic analysis • Results not significantly different from other subjects in the same dosing group at the same time points
Pre-dose sample 5 min after start of infusion	1 sample from 1/18 subjects	Acceptable • Not excluded from analysis
Sampling - Urine		
Missing volume or sample not received	1-3 samples each (0-2, 2-4, 6-8, 8-10, or 10-12 h after first dose) from 10/18 subjects 1-2 samples each (0-2, 2-4, 4-6, 8-10, 12-24, or 24-48 h after last dose) from 13/18 subjects All samples after last dose from 1/18 subjects	**Unacceptable** • Results missing for following subjects: 1001: Day 1: 8-10, 10-12 h Day 14: 4-6 h 1002: Day 1: 6-8 h Day 14: 4-6 h 1004: Day 1: 0-2 h Day 14: 4-6 h 1005: Day 1: 2-4 h -- 1007: -- Day 14: 12-24 h 1008: -- Day 14: 2-4 h 2001: -- Day 14: 0-2, 8-10 h 2002: -- Day 14: 2-4 h 2004: -- Day 14: 4-6 h 2006: Day 1: 4-6, 6-8, 8-10 h Day 14: 24-48 h 2007: Day 1: 4-6, 6-8 h Day 14: 24-48 h 2008: Day 1: 4-6, 6-8 h Day 14: 24-48 h 3001: -- Day 14: all 3005: Day 1: 4-6, 6-8, 8-10 h Day 14: 12-24 h 3006: Day 1: 4-6, 6-8, 8-10 h -- 3007: Day 1: 4-6, 6-8, 8-10 h -- • Amount recovered in urine underestimated, including subjects who received the proposed therapeutic dose 600 mg Q12 (1-3 samples each from 3/6 subjects after first dose and from 6/6 subjects after last dose)
Bioanalytical - Plasma		
No phosphatase inhibitor added (i.e., unstabilized)	2 samples each (36 and 48 h after last dose) from 3/18 subjects	Acceptable • Results similar to other subjects in the same dosing group at the same time points
Missing results	8 samples total from 8/18 subjects	Acceptable • Missing results not anticipated to have significant impact, including subjects who received the proposed therapeutic dose 600 mg Q12 (pre-dose, and 0.5 h and three 24 h samples after last dose total from 5/6 subjects)

Pharmacokinetic parameters of PPI-0903, PPI-0903M, and PPI-0903M-1 following single and multiple dose administration are listed in **Table 7** and **Table 8**, respectively. (Note: Estimates of V_{ss} were not provided for PPI-0903M or PPI-0903M-1 by the Sponsor.) Concentration-time profiles of PPI-0903M and PPI-0903M-1 are displayed in **Figures 1-2** for single doses and **Figures 3-4** for multiple doses.

Table 7. Geometric mean (geometric %CV) pharmacokinetic parameters of PPI-0903, PPI-0903M, and PPI-0903M-1 following **single doses** of PPI-0903 as 1-hour IV infusions

Parameter	50 mg (n=6)	100 mg (n=6)	250 mg (n=6)	500 mg (n=6)	750 mg (n=6)	1000 mg (n=6)
PPI-0903						
C_{max} (µg/mL)	0.18 (16.7)	0.31 **(68.3)**	1.09 (27.0)	1.61 (36.9)	3.24 (41.7)	4.27 (23.2)
T_{max} (h)	0.44 **(58.8)**	0.44 **(58.2)**	0.52 **(67.7)**	0.60 (33.5)	0.42 (44.2)	0.63 **(63.4)**
AUC_{inf} (µg*h/mL)	0.14 (16.9)	0.25 **(71.6)**	0.82 (27.2)	1.17 (30.5)	2.90 (34.2)	3.29 (20.8)
$t_{1/2}$ (h)	0.07 (–)[a]	0.10 **(77.9)**	0.11 (–)[a]	0.12 (43.0)	3.60 (23.7)	0.76 **(90.0)**
V_{ss} (L)	34.6 (–)[a]	38.9 **(59.5)**	37.0 (–)[a]	55.0 (25.6)	233.7 (48.4)	72.1 **(75.7)**
CL (L/h)	350.5 (16.9)	396.8 **(71.6)**	305.6 (27.2)	429.3 (30.5)	258.7 (34.2)	304.4 (20.8)
CL_r (L/h)	0 (–)	0 (–)	0 (–)	0 (–)	0.012 (27.6)	0.012 (38.8)
% Urinary Recovery	0 (–)	0 (–)	0 (–)	0 (–)	0.0 (0.2)	0.0 (22.4)
PPI-0903M						
C_{max} (µg/mL)	1.49 (18.1)	2.94 (40.8)	9.92 (19.8)	16.53 (13.7)	22.96 (23.1)	30.23 (15.8)
T_{max} (h)	0.97 (9.0)	0.97 (9.2)	0.99 (13.8)	1.02 (8.6)	1.00 (9.2)	0.94 (4.2)
AUC_{inf} (µg*h/mL)	3.89 (21.5)	6.57 (26.1)	22.9 (26.4)	44.7 (6.6)	56.9 (18.8)	80.5 (11.3)
$t_{1/2}$ (h)	2.02 (7.9)	2.20 (20.1)	2.31 (12.8)	2.51 (11.4)	2.61 (11.6)	2.89 (4.9)
V_z[b] (L)	33.11 –	42.71 –	32.15 –	35.73 –	43.74 –	45.71 –
CL (L/h)	11.34 (21.5)	13.45 (26.1)	9.65 (26.4)	9.87 (6.6)	11.64 (18.8)	10.97 (11.3)
CL_r (L/h)	5.4 (39.0)	5.52 (40.1)	4.40 (42.5)	5.56 (15.6)	6.29 (27.7)	7.75 (17.9)
% Urinary Recovery	47.5 (28.2)	41.1 (35.9)	45.7 (42.9)	56.3 (10.2)	54.1 (25.0)	70.7 (10.4)
PPI-0903M-1						
C_{max} (µg/mL)	0.15 (26.3)	0.67 (17.2)	0.69 (40.6)	2.17 (28.4)	2.79 (24.6)	2.93 (13.5)
T_{max} (h)	1.85 **(73.7)**	0.97 (9.2)	1.29 (25.2)	1.05 (12.9)	1.14 (18.1)	1.04 (20.8)
AUC_{inf} (µg*h/mL)	1.29 (26.1)	3.34 (21.6)	5.76 (25.0)	13.67 (10.1)	18.80 (28.8)	21.02 (19.8)
$t_{1/2}$ (h)	3.49 (21.3)	3.71 (35.2)	4.03 (6.8)	4.78 (30.4)	4.94 (15.1)	6.83 (25.4)
V_z[b] (L)	177.1 (33.3)	145.6 (39.3)	229.5 (19.1)	229.2 (31.3)	258.5 (13.9)	425.9 (22.6)
CL (L/h)	35.18 (26.1)	27.23 (21.6)	39.46 (25.0)	33.26 (10.1)	36.28 (28.8)	43.27 (19.8)
CL_r (L/h)	2.82 (22.7)	1.84 (42.6)	2.68 (35.0)	2.70 (17.8)	2.59 (43.8)	3.61 (20.6)
% Urinary Recovery	7.8 (4.6)	6.7 (36.0)	6.8 (22.1)	8.1 (22.3)	7.1 (31.2)	8.3 (14.8)

[a] *no SD estimate because N=1*
[b] *Geometric means for V_z calculated by the Reviewer*
Bolded blue font indicates geometric %CV value **greater than 50%**
Bolded red font indicates geometric %CV value **greater than 75%**

Table 8. Geometric mean (geometric %CV) pharmacokinetic parameters of PPI-0903, PPI-0903M, and PPI-0903M-1 following **single** (Day 1) **and multiple doses** (Day 14 or 7) of PPI-0903 as 1-hour IV infusions

Parameter	300 mg Q12 (n=6)		600 mg Q12 (n=6)		800 mg Q24 (n=6)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 7
PPI-0903						
C_{min} (µg/mL)	–	0 (–)	–	0 (–)	–	0 (–)
C_{max} (µg/mL)	1.46 (27.6)	1.37 (43.8)	3.25 (48.4)	3.08 (40.1)	3.05 (16.8)	4.05 (29.2)
T_{max} (h)	0.76 (16.7)	0.57 **(54.3)**	0.42 (44.2)	0.51 **(65.8)**	0.56 **(56.1)**	0.57 **(52.0)**
AUC_{inf} or AUC_{τ} (µg*h/mL)	1.11 (39.7)	1.10 (44.3)	3.01 **(87.6)**	2.41 (42.5)	2.38 (12.9)	2.90 (39.2)
$t_{1/2}$ (h)	0.18 **(122.3)**	0.18 **(51.1)**	0.29 (26.1)	0.15 **(71.3)**	0.20 **(57.4)**	0.20 **(54.2)**
V_{ss} (L)	44.6 **(55.3)**	32.8 (48.2)	47.0 **(219.2)**	29.3 (39.7)	49.0 **(63.3)**	34.2 **(64.9)**
CL (L/h)	270.3 (39.7)	273.1 (44.3)	199.2 **(87.6)**	248.7 (42.5)	336.1 (12.9)	275.6 (39.2)
CL_r (L/h)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
% Urinary Recovery	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)	0 (–)
Accumulation Ratio	–	0.99 (21.4)	–	0.80 **(99.1)**	–	1.21 (40.6)
PPI-0903M						
C_{min} (µg/mL)	–	0.19 **(54.4)**	–	0.39 (40.7)	–	0.02 (47.2)
C_{max} (µg/mL)	9.96 (7.7)	8.39 (22.9)	18.96 (3.9)	21.02 (20.1)	29.30 (19.1)	31.43 (8.2)
T_{max} (h)	1.00 (10.2)	0.97 (8.6)	1.02 (13.4)	0.97 (8.6)	0.92 (20.4)	1.02 (8.6)
AUC_{inf} or AUC_{τ} (µg*h/mL)	25.54 (16.4)	24.10 (16.0)	56.08 (19.5)	55.69 (16.4)	71.96 (12.4)	72.94 (22.5)
$t_{1/2}$ (h)	2.52 (18.2)	2.60 (16.1)	1.57 (25.4)	2.63 (18.0)	2.16 (7.2)	2.62 (10.2)
V_z[a] (L)	37.76 –	39.72 –	21.38 –	34.64 –	30.56 –	36.69 –
CL (L/h)	10.37 (16.4)	11.00 (16.0)	9.45 (19.5)	9.52 (16.4)	9.82 (12.4)	9.68 (22.5)
CL_r (L/h)	3.65 **(64.7)**	4.37 (33.7)	3.96 (40.2)	6.74 (47.2)	4.51 (35.8)	3.80 (37.5)
% Urinary Recovery	34.6 **(59.6)**	39.8 (25.5)	40.9 (32.3)	69.0 (25.9)	45.0 (22.1)	39.3 (24.7)
Accumulation Ratio	–	0.97 (18.5)	–	1.02 (12.5)	–	1.00 (12.6)
PPI-0903M-1						
C_{min} (µg/mL)	–	0.27 (26.4)	–	0.63 (44.7)	–	0.08 (26.7)
C_{max} (µg/mL)	1.08 (20.0)	1.26 (10.7)	2.63 (32.0)	3.54 (18.2)	2.56 (11.4)	2.90 (26.3)
T_{max} (h)	1.22 (20.2)	1.30 (28.3)	1.25 **(103.4)**	1.11 (21.5)	1.31 (34.2)	1.05 (12.1)
AUC_{inf} or AUC_{τ} (µg*h/mL)	7.91 (12.8)	8.03 (15.0)	15.55 (21.4)	18.53 (25.5)	18.06 (9.9)	20.39 (18.7)
$t_{1/2}$ (h)	4.58 (14.8)	6.85 (19.7)	3.31 (43.5)	6.82 (8.8)	3.98 (19.5)	6.86 (5.9)
V_z[a] (L)	228.1 (16.1)	252.9 (17.6)	167.3 (34.1)	211.4 (33.0)	231.3 (13.9)	334.3 (17.7)
CL (L/h)	34.51 (12.8)	33.96 (15.0)	35.09 (21.4)	29.44 (25.5)	40.27 (9.9)	35.67 (18.7)
CL_r (L/h)	2.00 **(55.7)**	1.56 (34.6)	1.60 **(84.6)**	1.84 (41.2)	1.41 **(91.6)**	1.27 (44.0)
% Urinary Recovery	4.8 (39.4)	4.6 (24.4)	3.7 **(62.8)**	6.1 (7.2)	3.0 **(81.8)**	3.5 (29.8)
Accumulation Ratio	–	1.24 (12.1)	–	1.45 (7.6)	–	1.11 (13.0)

[a] *Geometric means for V_z calculated by the Reviewer*

Bolded blue font indicates geometric %CV value **greater than 50%**

Bolded red font indicates geometric %CV value **greater than 75%**

Figure 1. Mean (standard error) concentration-time profiles of **PPI-0903M** following single doses of PPI-0903 as a 1-hour IV infusion

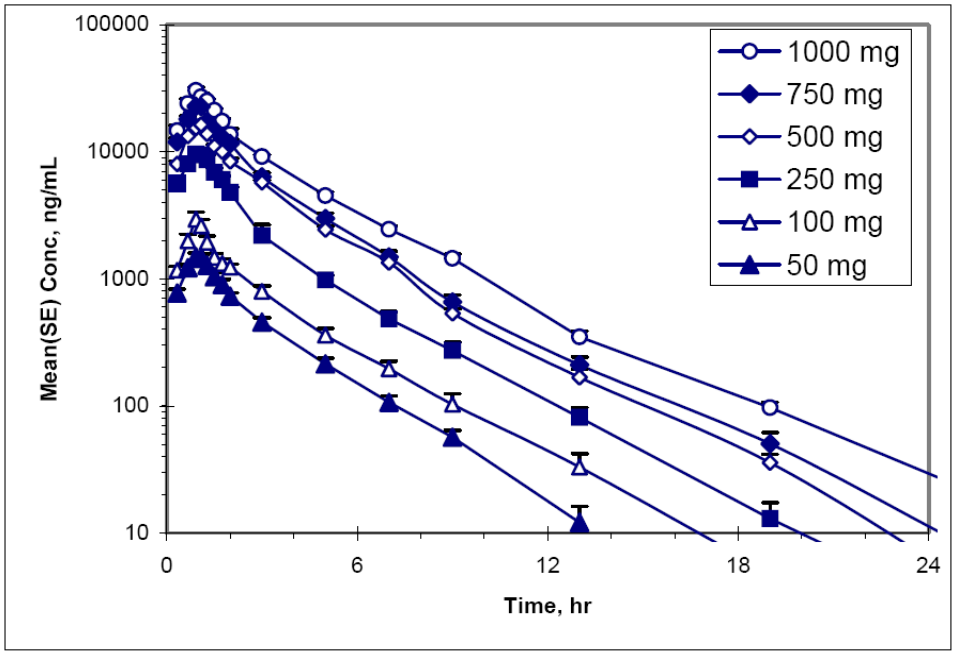


Figure 2. Mean (standard error) concentration-time profiles of **PPI-0903M-1** following single doses of PPI-0903 as a 1-hour IV infusion

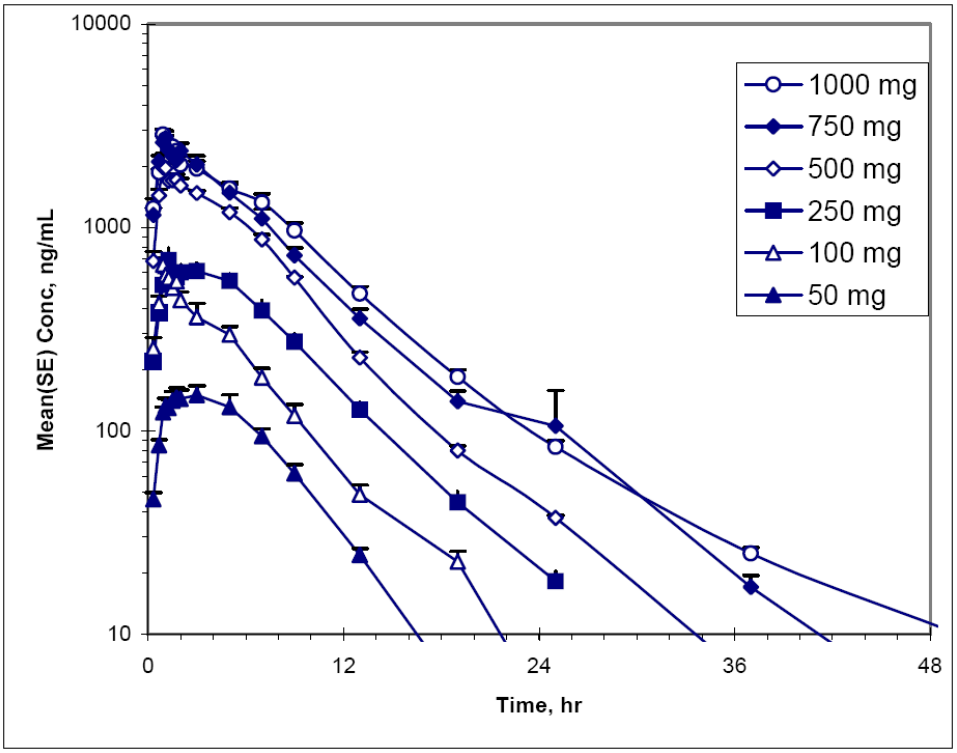
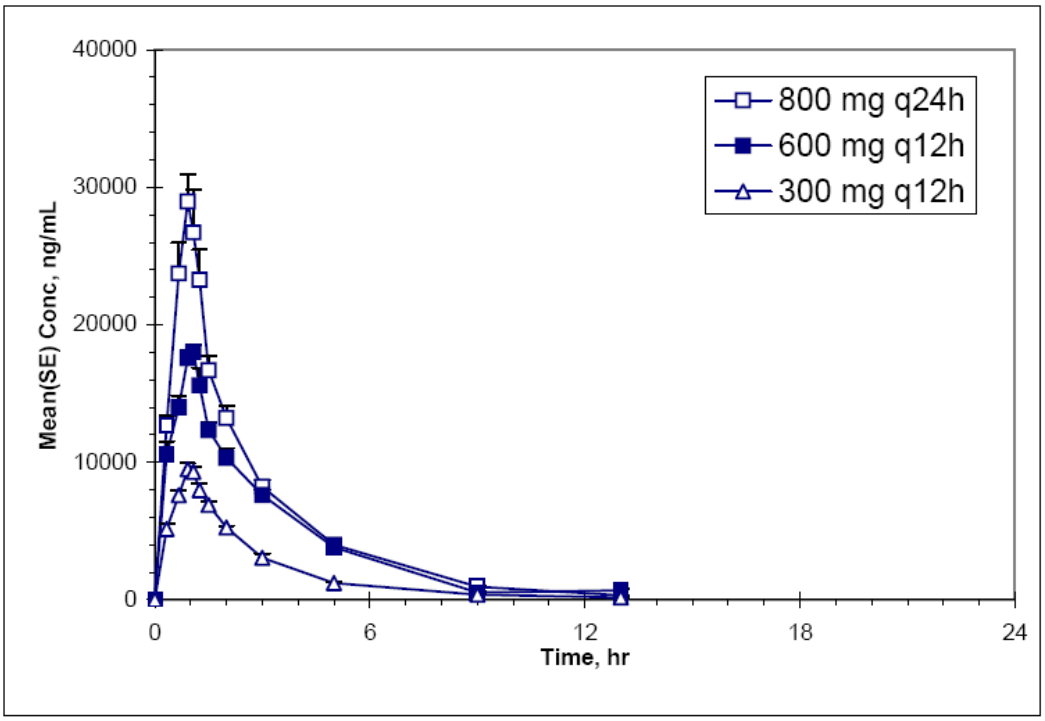


Figure 3. Mean (standard error) concentration-time profiles of **PPI-0903M** following multiple doses of PPI-0903 as a 1-hour IV infusion on **A) Day 1** and **B) Day 14** (for Q12) **or 7** (for Q24)

A)



B)

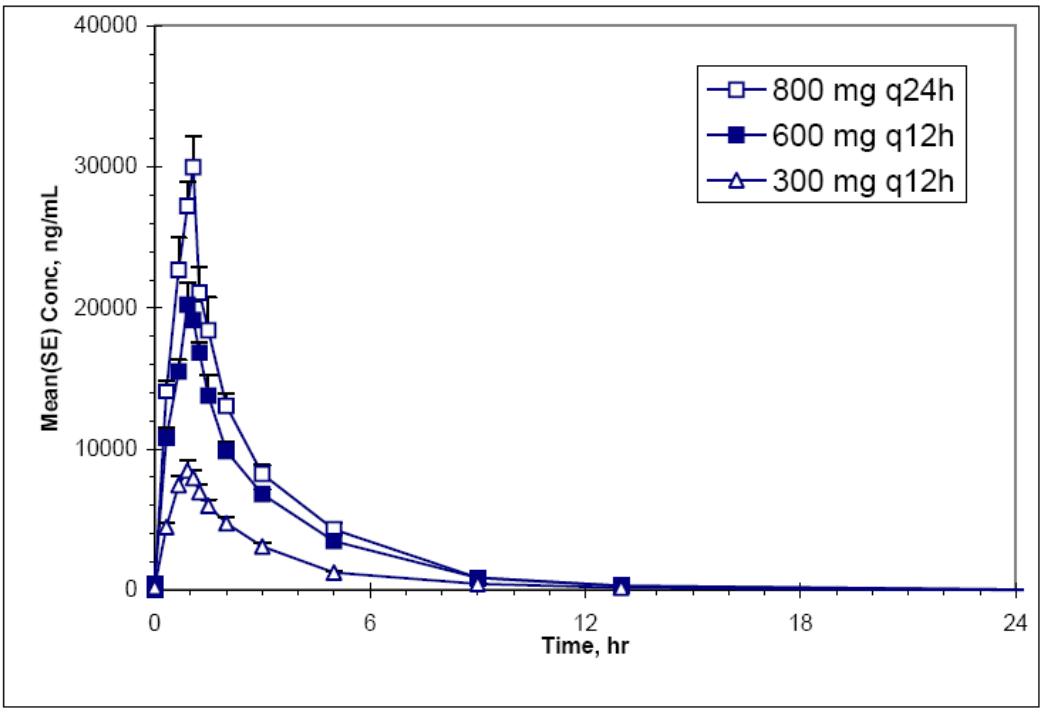
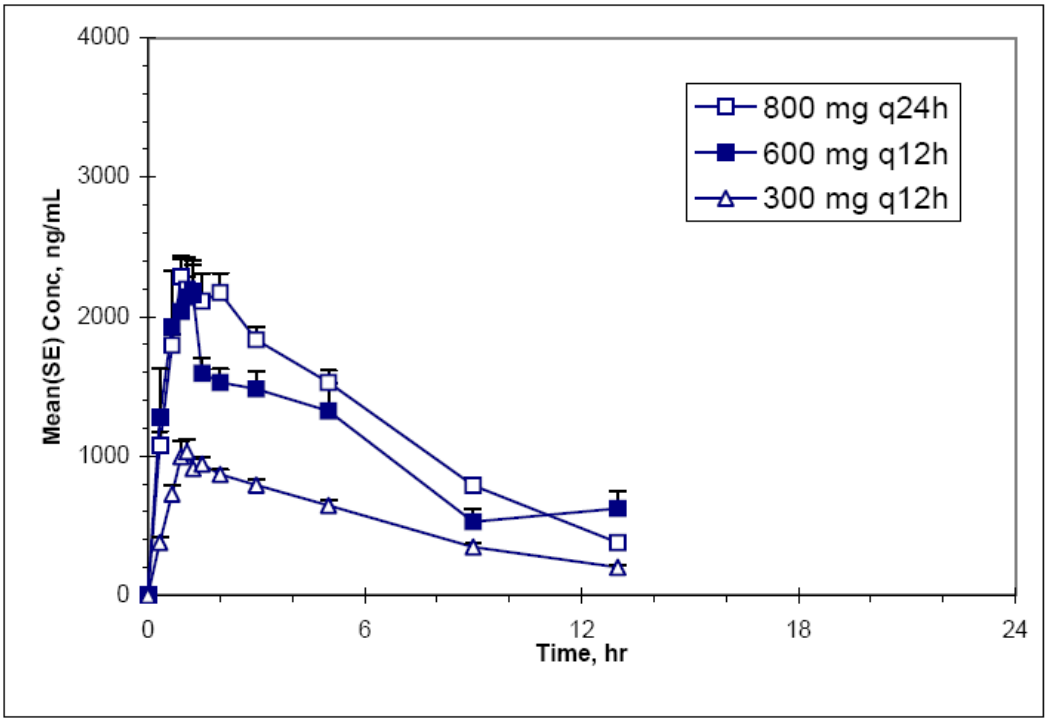
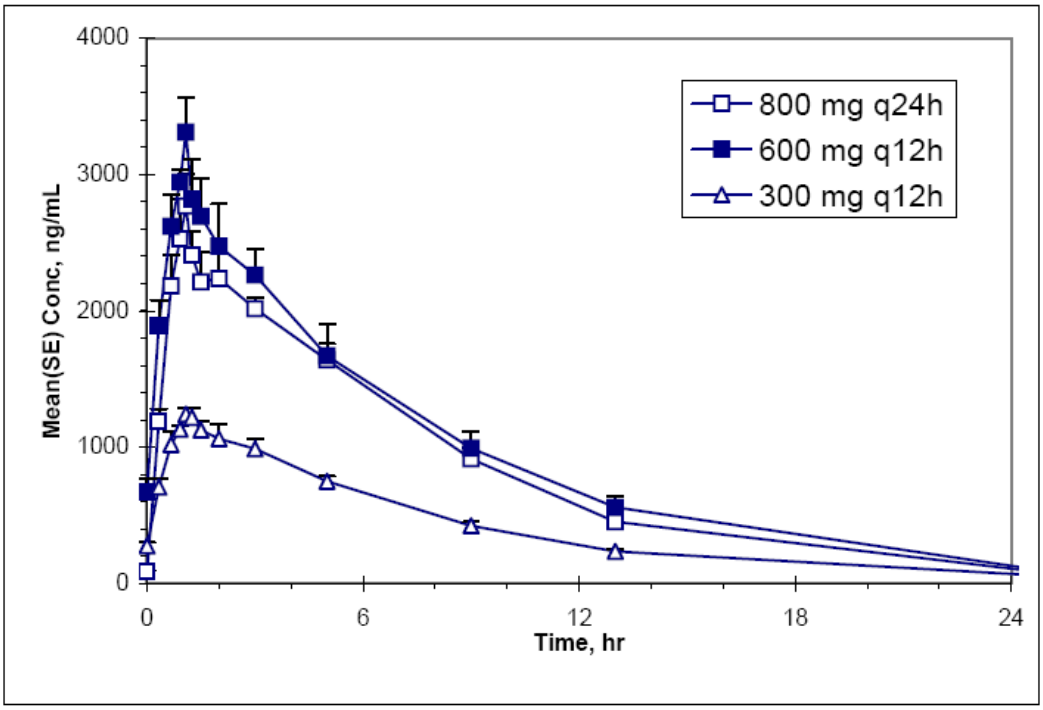


Figure 4. Mean (standard error) concentration-time profiles of **PPI-0903M-1** following multiple doses of PPI-0903 as a 1-hour IV infusion on **A) Day 1** and **B) Day 14** (for Q12) **or 7** (for Q24)

A)



B)



(i) Single-Dose, PPI-0903 (prodrug): Geometric mean values for C_{max} and AUC_{inf} increased relatively in a dose-proportional manner. T_{max} for PPI-0903 occurred during the 1 hour IV infusion, although values were variable between subjects. Conversion to the active PPI-0903M was rapid, as the elimination $t_{1/2}$ for PPI-0903 was ≤15 minutes or otherwise undeterminable for doses 50-500 mg. The $t_{1/2}$ for the highest dose of 1000 mg ranged approximately 0.5-2 hours, while values were unexpectedly higher at the lower 750 mg dose with 2.5-4.5 hours for all subjects in this group. V_{ss} could only be determined in several subjects for doses 50-250 mg, while geometric means were 55.0 L for 500 mg and 72.1 L for the highest dose of 1000 mg. For the 750 mg group, all subjects had the highest V_{ss} values of all other doses, ranging 150-260 L. CL did not appear to vary with dose, with geometric means ranging 258.7-429.3 L/h. CL_r for PPI-0903 could not be calculated as no PPI-0903 was recovered in urine. (Note: Due to rapid biotransformation of prodrug, pharmacokinetic parameters that involve proper characterization of the terminal phase were interpreted with caution.)

Reviewer Comment: High geometric %CV (i.e., >50% and >75%) observed with PPI-0903 following single dose administration is acceptable because 1) variability was a product of missing data from several subjects for the lower dosing groups, and 2) variability is reasonable as PPI-0903 is rapidly converted to PPI-0903M, making certain pharmacokinetic parameters difficult to determine.

Reviewer Comment: It is unclear why the PPI-0903 $t_{1/2}$ and V_{ss} for the 750 mg group was uncharacteristically and consistently the highest of all other doses, including the highest dose of 1000 mg. It should be noted that concentrations were detectable up to 6 hours post-dose for subjects in the 750 mg group, while PPI-0903 was generally BLQ at ≤1 hour post-dose for all other dosing groups. Regardless, this discrepancy with the 750 mg group is inconsequential as PPI-0903 is simply the prodrug, and $t_{1/2}$ and V_{ss} data for PPI-0903 is not pertinent.

(ii) Single-Dose, PPI-0903M (active metabolite): Geometric means for C_{max} and AUC_{inf} of the active PPI-0903M increased proportionally with dose in a linear fashion, and T_{max} occurred around the end of 1-hour IV infusion. Elimination $t_{1/2}$ appeared to trend higher with increasing dose, but was generally between 2-3 hours. Both geometric mean V_z and CL did not vary with dose, and ranged 32.15-45.71 L and 9.65-13.45 L/h, respectively. Geometric mean Cl_r was approximately 5 L/h for doses 50-500 mg, increasing to 6.29-7.25 L/h for doses 750-1000 mg. Similarly, approximately 50% of PPI-0903M was recovered in urine, with 70.7% at the highest dose of 1000 mg. Variability (as geometric %CV) for all single-dose pharmacokinetic parameters were <50%.

(iii) Single-Dose, PPI-0903M-1 (inactive, open-ring metabolite of PPI-0903M): Geometric mean C_{max} and AUC_{inf} of the major metabolite M-1 increased relatively in proportion with dose, and T_{max} occurred generally between 1-2 hours across doses. Elimination $t_{1/2}$ of M-1 similarly trended higher with increasing dose, ranging 3.49-6.83 hours for doses 50-1000 mg. Both geometric mean V_z and CL did not vary significantly with dose, and ranged 145.6-425.9 L and 27.23-43.27 L/h, respectively. CL_r for M-1 was minimal, comparatively to the active PPI-0903M, ranging 2.84-3.61 across doses with 6.7-8.3% recovered in urine. AUC_{inf} ratio to the active PPI-0903M (calculated by the Reviewer) did not vary with dose and is reported as geometric mean for 50, 100, 250, 500, 750, and 1000 mg, respectively: 0.33, 0.51, 0.25, 0.31,

0.33, and 0.26. There were no single-dose pharmacokinetic parameters with geometric %CV >75%.

(iv) Multiple-Dose, PPI-0903 (prodrug): C_{max} and AUC (i.e., AUC_{inf} for single dose and AUC_{τ} for multiple dose) did not change significantly with repeat dosing (Day 14 or Day 7 versus Day 1), with minor accumulation (geometric mean, 21%) observed for the 800 mg Q24 regimen. T_{max} was variable among subjects but generally occurred during the 1-hour IV infusion for all dosing regimens. Estimates of elimination $t_{1/2}$ did not vary with multiple doses but were also variable, particularly for the 300 mg Q12 regimen on Day 1 due to Subject 1008 (3 minutes versus approximately 10-20 minutes for all other subjects). Geometric mean V_{ss} and CL were not significantly different between single and repeat doses, although V_{ss} trended lower on Day 14 or 7 versus Day 1. Estimates for V_{ss} and CL were also variable, particularly for the 600 mg Q12 regimen (the proposed therapeutic regimen) on Day 1 due to Subject 2004 and Subject 2008. PPI-0903 was not recovered in urine and CL_r was non-existent. (Note: Due to rapid biotransformation of prodrug, pharmacokinetic parameters that involve proper characterization of the terminal phase were interpreted with caution.)

Subject 2004 had PPI-0903 concentrations for Day 1 that were lower than others in the same dosing group at nearly every time point, which resulted in low AUC_{inf} of 1.15 (versus geometric mean, 3.01 μg*h/mL) and high CL of 521.5 L/h (versus geometric mean, 199.2 L/h). Subject 2008 unusually had additional peaks in PPI-0903 concentrations on Day 1 at later time points, 4 and 12 hours post-dose (1.92 and 0.09 μg/mL, respectively), after previously undetectable levels. This considerably impacted estimates of AUC_{inf} (7.87 versus geometric mean 3.01 μg*h/mL), CL (75.96 versus geometric mean 199.2 L/h), and V_{ss} (265.8 versus geometric mean 47.0 L) for Subject 2008. Because of the outliers in AUC_{inf} from Subject 2004 and Subject 2008, the geometric %CV for the accumulation ratio for the 600 mg Q12 regimen (Subject 2004, 2.37; Subject 2008, 0.30) was particularly high (i.e., >75%).

(v) Multiple-Dose, PPI-0903M (active metabolite): C_{max} and AUC did not change significantly with repeat dosing, with minimal accumulation (geometric mean, <5%) for all dosing regimens. Similarly, C_{min} (i.e., trough concentration) did not vary significantly with each repeat dose, and geometric means for the final dose were 0.19 and 0.39 μg/mL for 300 and 600 mg Q12, respectively, while considerably lower with 0.02 μg/mL for 800 mg Q24 due to less frequent dosing. T_{max} generally occurred around the end of 1-hour IV infusion for both single and multiple doses across regimens. Geometric mean $t_{1/2}$, V_z, and CL were not significantly different between single and multiple dosing, and ranged 2.60-2.63 hours, 34.64-39.72 L, and 9.52-11.00 L/h, respectively, across regimens for Day 14 or 7. Variability (as geometric %CV) for all multiple-dose pharmacokinetic parameters were <75%.

Reviewer Comment: In light of the considerable number of protocol deviations that occurred with urine sampling for each multiple-dose regimen in combination with higher than acceptable geometric %CV for assay of urine samples, urinary pharmacokinetic results of PPI-0903M for multiple-dose regimens will be disregarded.

(vi) Multiple-Dose, PPI-0903M-1 (inactive, open-ring metabolite of PPI-0903M): C_{max} and AUC appeared to trend higher with repeat dosing, with geometric means for accumulation of 11-

45% across dosing regimens. C_{min} did not vary significantly with each repeat dose, and geometric means for the final dose were 0.27 and 0.63 μg/mL for 300 and 600 mg Q12, respectively, while considerably less with 0.08 μg/mL for 800 mg Q24. T_{max} occurred generally between 1-2 hours for both single and multiple doses across regimens, except for Subject 2008 whose Day 1 T_{max} was delayed at 5 hours post-dose. Elimination $t_{1/2}$ appeared to be longer with repeat dosing (approximately 7 hours across regimens for Day 14 or 7), but this is likely due to extended sampling following the final dose (beyond 12 hours post-dose) that allowed better characterization of the terminal phase and thus, more accurate determination of the elimination rate constant. Geometric mean V_z and CL did not differ significantly with repeat dosing, although V_z appeared to trend higher, and ranged 211.4-334.3 L and 29.44-35.67 L/h, respectively, across regimens for Day 14 or 7. AUC_{inf} ratio to the active PPI-0903M (calculated by the Reviewer) did not vary from single doses and is reported as geometric mean for 300 mg Q12, 600 mg Q12, and 800 mg Q24, respectively, on Day 14 or 7: 0.33, 0.33, and 0.28.

Reviewer Comment: In light of the considerable number of protocol deviations that occurred with urine sampling for each multiple-dose regimen in combination with higher than acceptable geometric %CV for assay of urine samples, urinary pharmacokinetic results of PPI-0903M-1 for multiple-dose regimens will be disregarded.

Safety: In Part 1 (single-dose), 10/36 (28%) subjects receiving PPI-0903 reported at least one adverse event compared to 3/13 (25%) subjects receiving placebo. All events were mild in severity; the most common event overall being headache (n=5; 4 active, 1 placebo). No consistent pattern in adverse event or severity of adverse event was detected.

In Part 2 (multiple-dose), 12/18 (67%) subjects receiving PPI-0903 reported at least one adverse event compared to 6/6 (100%) subjects receiving placebo. The most common event overall was bruising of the arm (n=8; 5 active, 3 placebo), while urine discoloration was the most common in those who received active drug (n=6/6, 600 mg Q12 group). All were mild in severity except for five adverse events in three subjects which were moderate in severity: rash (n=2; 600 mg Q12), injection site inflammation (n=1; 600 mg Q12), postural hypotension (n=1; 600 mg Q12), and vasovagal symptoms (n=1; placebo). Urine discoloration, change in urine odor, change in body odor, rash, thrombophlebitis, and injection site inflammation occurred in greater frequency in those who received PPI-0903 than placebo.

Darkening of urine color was reported by 100% of those receiving PPI-0903 600 mg Q12 × 14 days, which contains the highest daily dose (1200 mg) and the highest cumulative dose (16,200 mg), but not at any other dose level or regimen. Of those in the 600 mg Q12 group, 67% additionally experienced a change in odor and 50% experienced a change in body odor. Urine discoloration and change in urine and/or body odor are considered related to study drug and may be due to excretion of PPI-0903 and/or its metabolites via urine and sweat.

Self-limiting rash (which resolved while continuing to receive PPI-0903) was reported in the 300 mg Q12 (n=1/6) and 600 mg Q12 (n=3/6) groups. Rash was considered unlikely to be related to study drug, however the possibility of an association with PPI-0903 could not be completely excluded given that β-lactams have been known to cause rash.

Injection site inflammation occurred in 300 mg Q12 (n=1/6) and 600 mg Q12 (n=1/6) groups and thrombophlebitis in the 600 mg Q12 group (n=1/6) only. A causal relationship to PPI-0903 could not be excluded due to the greater frequency of occurrence versus placebo; injection site inflammation and thrombophlebitis may be directly related to PPI-0903 and/or the infusion process in general.

No clinically significant change in biochemistry, hematology, coagulation, or urinalysis parameter was noted.

SPONSOR'S CONCLUSIONS: Following single (50, 100, 250, 500, 750 and 1000 mg) and multiple (300 mg Q12 ×14 days, 600 mg Q12 ×14 days, and 800 mg Q24 ×7 days) dose administration of PPI-0903 in healthy volunteers:

- The pharmacokinetics of PPI-0903, PPI-0903M, and PPI-0903M-1 were linear over the dose range and dosing duration.
- C_{max} and AUC for PPI-0903, PPI-0903M, and PPI-0903-M1 increased proportionately with dose and were independent of dose duration.
- Relative exposure of PPI-0903M and PPI-0903M-1 to prodrug PPI-0903 was independent of dose and dose duration.
- CL for prodrug PPI-0903 was high and independent of dose or dose duration (averaging 336 L/h for single dose and 261 L/h for multiple dose), consistent with rapid biotransformation to the active metabolite, PPI-0903M.
- CL for PPI-0903M (averaging 11 L/h for single doses and 10 L/h for multiple doses) and PPI-0903M-1 (averaging 35 L/h for single doses and 32 L/h for multiple doses) was independent of dose or dose duration.
- PPI-0903 $t_{1/2}$ was independent of dose and dose duration, averaging 0.16-0.43 hours.
- The $t_{1/2}$ for PPI-0903M (averaging 2.41 h for single dose and 2.61 h for multiple dose) and PPI-0903M-1 (averaging 4.51 h for single dose and 6.84 h for multiple dose) was independent of dose and dose duration; no accumulation was observed for PPI-0903M with Q12 and Q24 dosing and modest accumulation for PPI-0903M-1 (34%).
- No PPI-0903 was excreted unchanged in urine for most subjects, while a significant percentage of PPI-0903M and a small percentage of PPI-0903M-1 were both detected in urine.
- PPI-0903 was safe and well-tolerated in all subjects at doses and dosing regiments that were evaluated; no dose-limiting toxicity was observed.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results. The following outlines outstanding issues with Study P903-01.

- ***High pharmacokinetic geometric %CV:*** Most pharmacokinetic data with geometric %CV values >75% were with the prodrug PPI-0903, due to its rapid bioconversion to active PPI-0903M, making determination of certain parameters difficult. High pharmacokinetic geometric %CV for PPI-0903 is acceptable, as these data will not be used for labeling purposes.
- ***Urine pharmacokinetic data:*** High analytical %CV values for assay of urine samples can be considered acceptable for Part 1 (single-dose) data. However, in combination with numerous urine samples missing from most subjects for each dosing group in Part 2 (multiple-dose), the validity of urinary pharmacokinetic data (likely underestimates) is questionable and

therefore, should be disregarded. Urinary excretion information for the proposed therapeutic 600 mg Q12 regimen will instead be obtained from the mass balance study (Study P903-13) for labeling purposes. However, if necessary, urinary excretion data may be obtained from 3/6 subjects in the 600 mg Q12 group who had complete urine collection without any missing samples from the 0-24 hour period (**Table 9**).

Table 9. Urine pharmacokinetic parameters of PPI-0903, PPI-0903M, PPI-0903M-1 following multiple doses of PPI-0903 600 mg Q12 as 1-hour IV infusions

	Day 14 Cl_r (L/h)		Day 14 % Urinary Recovery	
	All subjects (n=6)	**Without missing samples[a] (n=3)**	**All subjects (n=6)**	**Without missing samples[a] (n=3)**
PPI-0903				
Geometric Mean	–	–	–	–
Mean	0.0	0.0	0.0	0.0
SD	0.0	0.0	0.0	0.0
PPI-0903M				
Geometric Mean	5.58	5.76	58.69	61.87
Mean	7.13	5.90	73.94	62.04
SD	4.37	1.52	45.92	5.60
PPI-0903M-1				
Geometric Mean	1.68	1.68	5.72	6.16
Mean	1.79	1.76	5.91	6.17
SD	0.61	0.58	1.48	0.51

[a] *Subjects 2001, 2002, and 2004 were excluded due to missing urine samples on Day 14: 2001, 0-2 and 8-10 hours; 2002, 2-4 hours; and 2004, 4-6 hours.*

For labeling, only steady-state pharmacokinetic data of PPI-0903M and PPI-0903M-1 for the proposed therapeutic 600 mg Q12 regimen will be used. Any high pharmacokinetic geometric %CV values >50% were largely observed with Day 1 and not Day 14. Pharmacokinetic data of prodrug PPI-0903 will not be included.

STUDY NO.: P903-13

A single-dose, open-label study to assess the metabolism and elimination of ceftaroline prodrug after intravenous administration of [^{14}C] ceftaroline fosamil in healthy subjects

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Date(s): 09 Jan 2008 – 07 Feb 2008
Investigator(s): S Flach, MD
Clinical Site(s): Covance Clinical Research Unit, Inc., Madison, WI
Analytical Site(s): (b) (4)

OBJECTIVE: To determine the rates and routes of elimination of radioactivity after intravenous (IV) administration of [^{14}C] ceftaroline fosamil in healthy subjects, and characterize and identify the metabolites of ceftaroline prodrug in plasma and excreta

METHODS

Study Design: P903-13 was a single-center, open-label, single-dose, mass balance study in male subjects (n=6). Subjects were to participate until one of the following criteria were met: 1) two consecutive urine and fecal samples contained a radioactivity level <3 times the background level or 2) cumulative radioactivity in the excreta for a day was <1% of the radioactivity of the administered dose.

Inclusion Criteria: Males, 18-45 years of age, 18-30 kg/m^2 (inclusive) in body mass index, and in good health as confirmed by medical history, physical exam, and laboratory evaluations were enrolled.

Treatment: Ceftaroline fosamil was administered as a single 1-hour IV infusion containing 600 mg of Ceftaroline for Injection with an additional 15 mg of [^{14}C] Ceftaroline fosamil (equivalent to 100 µCi of radioactivity). A total of 20 mL of [^{14}C] ceftaroline fosamil IV dosing solution (30 mg/mL; 5 µCi/mL) was added to an infusion bag containing 250 mL of 0.9% Sodium Chloride for Injection, for final drug and radioactive concentrations of 2.3 mg/mL and 0.4 µCi/mL, respectively.

Subjects received the single IV infusion after a standard meal. Concomitant medications, including over-the-counter drugs and vitamin or herbal supplements, were prohibited within 14 days prior to dose administration. No hormonal drug products were permitted from 30 days before dosing. Caffeine or grapefruit-containing products were also prohibited within 48 hours prior to dose and alcohol consumption within 72 hours.

Sample Collection: Plasma, urine, and fecal samples were collected (**Table 1**) and analyzed for pharmacokinetic purposes.

Table 1. Pharmacokinetic sampling scheme for single 1-hour IV infusion of [^{14}C] ceftaroline fosamil

Plasma	• Pre-dose • 20, 40, 60 (immediately before end of infusion), 65, and 75 min, and at 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, 144, and 168 h AFTER START of infusion
Urine	• Pre-dose (-12 to 0 h) • 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 h AFTER START of infusion
Feces	• Pre-dose (-24 to 0 h) • 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 h AFTER START of infusion

Analytical Methods: Pharmacokinetic samples were analyzed for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 by validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays for plasma (Method 3; PRD-RPT-BDM-00077, 2009) and urine (Method 4; PRD-RPT-BDM-00080, 2008) (**Table 2**). Plasma concentrations below the limit of quantification (BLQ) were treated as zero for pharmacokinetic analysis.

Table 2. Bioanalytical results of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma and urine

Criterion	Ceftaroline fosamil	Ceftaroline	Ceftaroline M-1	Comments
PLASMA				
Range	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	0.05-20 µg/mL (1:10 dilution tested with 16 µg/mL)	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	Satisfactory
LLOQ	0.05 µg/mL	0.05 µg/mL	0.05 µg/mL	Satisfactory
Linearity	R^2 ≥0.9903	R^2 ≥0.9894	R^2 ≥0.9942	Satisfactory
Accuracy	Within ±14.3%	Within ±10.4%	Within ±12.7%	Satisfactory
Precision	≤10.5 %CV	≤4.8 %CV	≤6.6 %CV	Satisfactory
Stability	• Study Dates: 09 Jan 2008 – 07 Feb 2008 • Analysis Dates: 6 Mar 2008 – 24 Apr 2008 • Stability: 526 days at -70 ºC			Satisfactory
URINE				
Range	0.5-5 µg/mL (1:5 dilution tested with 3.8 µg/mL)	0.5-50 µg/mL (1:9 dilution tested with 38 µg/mL)[a]	0.5-50 µg/mL (1:9 dilution tested with 38 µg/mL)[a]	Satisfactory
LLOQ	0.5 µg/mL	0.5 µg/mL	0.5 µg/mL	Satisfactory
Linearity	R^2 = 0.9960	R^2 ≥0.9874	R^2 ≥0.9884	Satisfactory
Accuracy	Within ±4.0%	Within ±8.7%	Within ±9.0%	Satisfactory
Precision	–	≤6.1 %CV	≤5.8 %CV	Satisfactory
Stability	• Study Dates: 09 Jan 2008 – 07 Feb 2008 • Analysis Dates: 5 Mar 2008 – 28 Apr 2008 • Stability: 469 days at -70 ºC			Satisfactory

[a] *Dilution integrity was evaluated further for ceftaroline and ceftaroline M-1 in urine during analysis for Study P903-13*

Total radioactivity counts in whole blood, plasma, urine, and fecal samples were determined using liquid scintillation counting (LSC). Metabolic profiling of ceftaroline fosamil in plasma, urine, and feces was determined using a non-validated radiometric high-performance liquid chromatography (HPLC) (Method 6; PRD-RPT-BDM-00204, 2009) (**Table 3**).

Table 3. Bioanalytical results of radioactivity for metabolic profiling of [^{14}C] ceftaroline fosamil

Criterion	Plasma	Urine	Feces
Recovery (Sample Preparation)	80.3%	–	79.8-82.7%
Recovery (HPLC)	90.8%	98.8-102.1%	82.2-84.0%
Radioactivity Count Efficiency	50.2% (mean of triplicate)		
Range	0.027-3.646 µCi/mL		
LLOQ	607.1 dpm		
Linearity	R^2 = 0.9961		
Accuracy	Within ±10.3%		

Pharmacokinetic Assessment: Pharmacokinetic parameters for ceftaroline fosamil, ceftaroline, ceftaroline M-1, and total radioactivity were determined using non-compartmental methods. Since doses were expressed in terms of anhydrous, acetate-free ceftaroline fosamil (MW, 684.68), corrections were made to the dose when calculating parameters for ceftaroline (MW, 604.70; 0.883 × ceftaroline fosamil dose) and ceftaroline M-1 (MW, 622.72; 0.909 × ceftaroline fosamil dose). Parameters included the following:

- C_{max}, peak observed plasma concentration
- AUC_{0-t}, area under the curve up to time corresponding to the last measurable concentration
- $AUC_{0-\infty}$, area under the curve from time 0 to infinity
- T_{max}, corresponding time of C_{max}
- $t_{1/2}$, elimination half-life
- CL, plasma clearance
- V_{ss}, steady-state volume of distribution
- Ae_{0-t}, cumulative amount of drug excreted during entire urine collection period from time 0 to time t
- CL_r, renal clearance

Statistical Methods: Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) were provided for continuous variables and frequency distribution (counts and percentages) were for categorical variables.

RESULTS

Study Population: All subjects were male (3 white, 3 black), 23-45 years of age, of 22.2-28.0 kg/m^2, and creatinine clearance (CrCL) 86.6-148.6 mL/min. The Sponsor indicates although some deviations from the study protocol did occur, they were few in number and were not related to study inclusion/exclusion criteria, conduct of the trial, subject management, or subject assessment; deviations were not considered significant or to have had a meaningful effect.

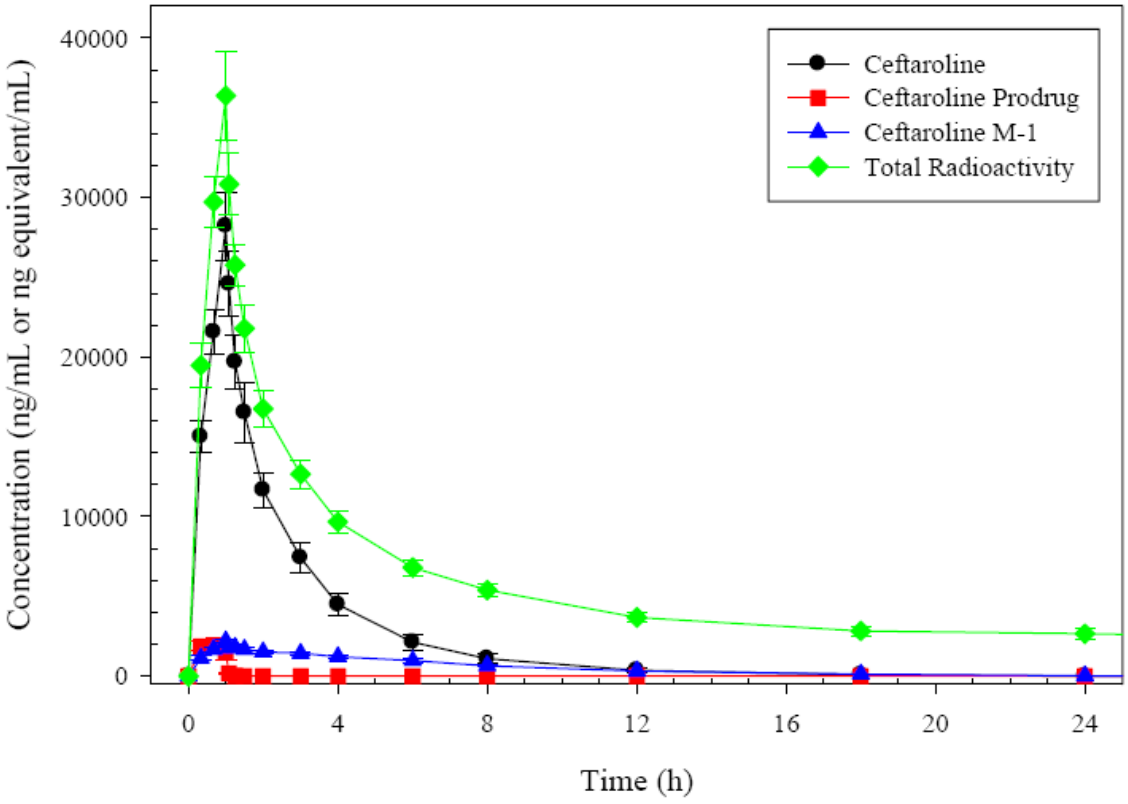
Pharmacokinetics: Pharmacokinetic parameters for ceftaroline fosamil, ceftaroline, ceftaroline M-1, and total radioactivity are listed in **Table 4**. Plasma concentration-time profiles of ceftaroline fosamil, ceftaroline, ceftaroline M-1, and total radioactivity are shown in **Figure 1**. Values for coefficient of variation (%CV) were <25% for all pharmacokinetic parameters, except T_{max} estimates for ceftaroline fosamil (34%).

Table 4. Mean ± SD pharmacokinetic parameters for ceftaroline fosamil, ceftaroline, ceftaroline M-1, and total radioactivity following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg

Parameter	Ceftaroline fosamil (n=6)	Ceftaroline (n=6)	Ceftaroline M-1 (n=6)	Total Radioactivity[a] (n=6)
C_{max} (µg/mL)	2.02 ± 0.31	27.35 ± 2.85	2.16 ± 0.16	35.78 ± 2.91
AUC_{0-t} (µg*h/mL)	1.56 ± 0.22	63.79 ± 6.30	13.16 ± 0.94	432.20 ± 45.64
$AUC_{0-\infty}$ (µg*h/mL)	–[b]	64.22 ± 6.38	13.67 ± 0.87	935.74 ± 175.79[c]
T_{max} (h)[d]	0.67 (0.33-0.98)	0.98 (0.95-1.08)	0.98 (0.95-1.08)	0.98 (0.95-1.08)
$t_{1/2}$ (h)	–[b]	2.60 ± 0.46	4.22 ± 0.33	214.61 ± 27.92[c]
CL (L/h)	–[b]	8.68 ± 0.88	41.77 ± 2.77	0.69 ± 0.12
V_{ss} (L)	–[b]	20.12 ± 1.37	248.18 ± 12.15	191.36 ± 18.78
Ae_{0-t} (% of dose)	0.00	65.02 ± 8.22[e]	5.66 ± 1.10	87.51 ± 3.94
CL_r (L/h)	0.00	5.56 ± 0.20[e]	2.47 ± 0.59	1.28 ± 0.10

[a] Concentration units are µg equivalent ceftaroline fosamil/mL.
[b] Could not be calculated.
[c] $AUC_{0-\infty}$ and $t_{1/2}$ for total radioactivity considered unreliable due to long terminal elimination half-life relative to the collection period.
[d] Reported as median (minimum-maximum).
[e] N=5; excluded Subject 13004 who had an unexpectedly high Ae value for ceftaroline for the 4-8 h urine collection interval (by 3-6 fold of other subjects). Including Subject 13004, mean estimates for Ae_{0-t} (%) and CL_r are 71.35 ± 17.18% and 6.22 ± 1.63 L/h, respectively, for ceftaroline.

Figure 1. Mean ±SD plasma concentrations for ceftaroline fosamil, ceftaroline, ceftaroline M-1, and total radioactivity following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg in healthy males (n=6)



(i) Ceftaroline fosamil (prodrug): Mean C_{max} was 2.02 μg/mL, occurring during the 1-hour IV infusion. Ceftaroline fosamil was rapidly converted to the active ceftaroline, and subsequently, parameters like $AUC_{0-\infty}$, $t_{1/2}$, V_{ss}, and CL could not be calculated since the terminal phase of the prodrug could not be characterized. No subject had measurable plasma concentrations after the 1.25 hour time point (i.e., 15 minutes after end of infusion). The prodrug was also not detected in any of the urine samples collected. These data are consistent with pharmacokinetic data obtained from the single- and multiple-dose pharmacokinetic study, P903-01.

(ii) Ceftaroline (active metabolite): Mean C_{max} was 27.35 μg/mL and T_{max} occurred around the end of 1-hour IV infusion. Ceftaroline was the predominant compound in plasma, with mean C_{max} 10 times that of the prodrug and an $AUC_{0-\infty}$ of 64.22 μg*h/mL. Mean elimination $t_{1/2}$ was 2.60 hours; mean CL and V_{ss} were 8.68 L/h and 20.12 L, respectively. These data are consistent with the single- and multiple-dose pharmacokinetic study, P903-01.

Ceftaroline was also the predominant compound in urine, with approximately 65% of the administered dose recovered in urine and mean Cl_r of 5.56 L/h. These results are higher than those reported from the single- and multiple-dose pharmacokinetic study, P903-01, however urinary pharmacokinetic data from P903-01 were considered underestimates due to a significant number of missing urine samples from most subjects, including single-dose urinary results for the 600 mg Q12 group.

(iii) Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline): Mean C_{max} was 2.16 μg/mL, approximately 8% of the C_{max} for active ceftaroline. M-1 was the second most prevalent compound in plasma, with mean $AUC_{0-\infty}$ of 13.67 μg*h/mL, approximately 20% of that for ceftaroline. T_{max} similarly occurred around the end of 1-hour IV infusion, while the elimination $t_{1/2}$ was slightly longer than ceftaroline with mean of 4.22 hours. Mean estimates of CL and V_{ss} were also greater than those for ceftaroline, with 41.77 L/h and 248.18 L, respectively. M-1 was minimally excreted in urine, composing of 5.66% of the administered dose and Cl_r of 2.47 L/h. These data are consistent with pharmacokinetic data obtained from the single- and multiple-dose pharmacokinetic study, P903-01 (not including urinary results from P903-01, which were underestimated).

(iv) Total radioactivity: Unchanged ceftaroline represented the majority of total radioactivity in plasma, as total radioactivity followed the time-course profile of ceftaroline. However, AUC_{0-t} estimation for total radioactivity was considerably higher than that of ceftaroline (432.20 versus 63.79 μg*h/mL, respectively) due to the long terminal $t_{1/2}$ relative to the extended collection period for radioactivity (concentrations were measurable in all subjects through last time point of 168 hours versus 18 hours for ceftaroline), which also impacted estimations of CL and V_{ss}. Plasma concentrations of total radioactivity were also 1.7-2.5 times that of whole blood (**Figure 2**), suggesting minimal penetration into red blood cells.

Mean recovery of radioactivity in urine and feces was 93.4 ± 3.1% (range, 87.5-95.9%) of the administered dose. Excretion was predominantly renal, as an average of 87.5 ± 3.9% was recovered in urine and 5.95 ± 2.93% in feces (**Figure 3**). Most of the administered radioactivity was recovered in the first 48 hours (~90%), and concentrations were quantifiable in urine and feces through the final collection in all subjects (maximum, 216 hours post-dose).

Figure 2. Mean ±SD concentration of radioactivity in plasma and whole blood (ng equivalents/mL) following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg in healthy males (n=6)

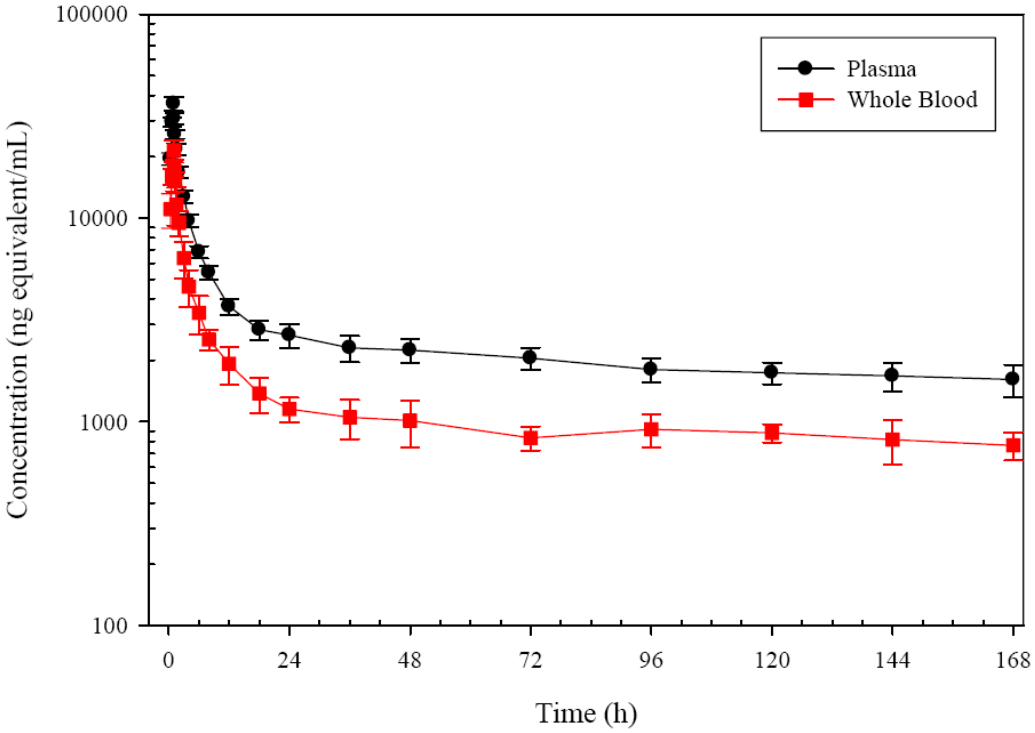
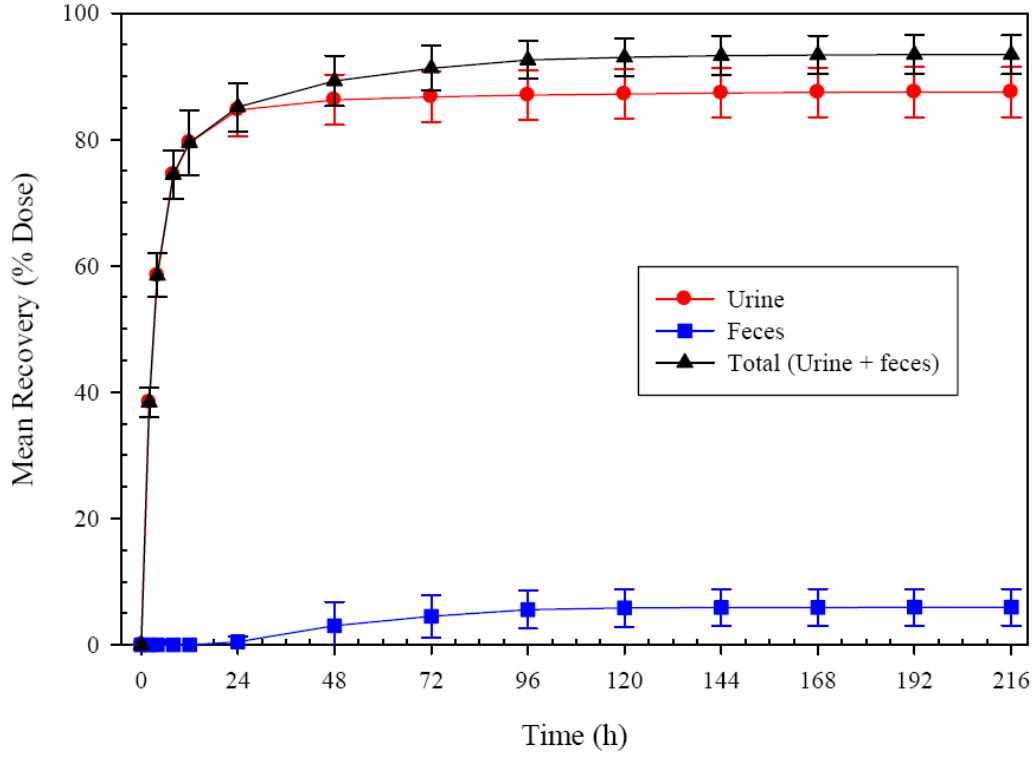


Figure 3. Mean ±SD cumulative percent of radioactive dose recovered in urine and feces following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg in healthy males (n=6)



Metabolic Profiling: Plasma samples at 1, 8, and 24 hour time points were analyzed for metabolite profiling; due to limited volume, plasma samples were pooled according to the time of collection. Urine samples at 0-2, 2-4, 4-8, 8-12, and 12-24 hour periods were analyzed for metabolic profiling as excretion in urine was almost complete in 24 hours (~85% of dose). A single fecal sample at 24-48 (n=3), 48-72 (n=2), or 72-96 (n=1) hour periods was evaluated for each subject. For identification of metabolites, only one pooled plasma sample (from 1-hour time point) and four urine samples (0-2 and 4-8 hours time points from Subject 13002; 0-2 and 8-12 hour time points from Subject 13004) were used.

In total, six chromatographic peaks were observed, three of which were ceftaroline fosamil (Peak 5), ceftaroline (Peak 6), and ceftaroline M-1 (Peak 4), while the remaining were minor unidentified metabolites (Peaks 1, 2, and 3) (**Table 5**). All six peaks were present in plasma, while five peaks in urine (no ceftaroline fosamil, Peak 5) and four peaks in feces (no ceftaroline M-1, Peak 4 and no ceftaroline fosamil, Peak 5) were observed.

Table 5. Chromatographic peaks observed in metabolite profiles in plasma, urine, and feces following single IV dose of [^{14}C] ceftaroline fosamil 600 mg in healthy males (n=6)

Chromatographic Peaks	Identity	Plasma	Urine	Feces
Peak 1	Minor unidentified metabolite	×	×	×
Peak 2	Minor unidentified metabolite	×	×	×
Peak 3	Minor unidentified metabolite	×	×	×
Peak 4	Ceftaroline M-1	×	×	–
Peak 5	Ceftaroline fosamil	×	–	–
Peak 6	Ceftaroline	×	×	×

(i) Plasma: Ceftaroline (Peak 6) was the major peak in the plasma metabolite profile, followed by ceftaroline fosamil (Peak 5) and ceftaroline M-1 (Peak 4). Identification of the remaining three chromatographic peaks (Peaks 1, 2, and 3) was not attempted, as plasma concentrations of each peak was relatively low and did not exceed 0.546 µg equivalent of ceftaroline fosamil/mL. The proposed metabolic pathway of ceftaroline fosamil to ceftaroline (by phosphatase enzymes *in vivo*) and ceftaroline M-1 (by hydrolysis of the β-lactam ring of ceftaroline) is pictured in **Figure 4.**

It was discovered that radioactivity recovery from 8-hour (35.6%) and 24-hour (<5%) plasma pools were drastically lower than that of the 1-hour plasma pool (80.3%) during sample preparation. Plasma protein appeared to be removed during sample preparation along with a portion of ceftaroline that was covalently bound to plasma protein, otherwise known as a ceftaroline-protein adduct (**Figure 5**). (Similar chemical bonding to plasma protein has been observed for β-lactam antibiotics such as cefotaxime and benzylpenicillin.) The chemical bond between ceftaroline and plasma protein was cleaved by alkaline hydrolysis, which was applied prior to regular sample preparation, and recovery of plasma radioactivity was subsequently improved (up to 88% for the 8-hour plasma pool). However, ceftaroline M-1 was not observed following alkaline hydrolysis, as additional bonds of the resulting ceftaroline M-1 appeared to be cleaved by alkaline hydrolysis as well. The final product from alkaline hydrolysis appeared to be a hydrophilic compound with low molecular weight, and was readily extracted in sample preparation. It is hypothesized that (similarly to the benzylpenicillin conjugate to plasma

protein) the ceftaroline conjugate to plasma protein is likely transformed slowly to ceftaroline M-1, then eventually excreted in urine. This slow transformation of the ceftaroline-protein adduct is also being implicated for producing the long terminal $t_{1/2}$ of plasma radioactivity. It should be noted that the proposed ceftaroline-protein adduct has also been observed in rat and monkey plasma.

Figure 4. Proposed metabolic pathway of ceftaroline fosamil in humans

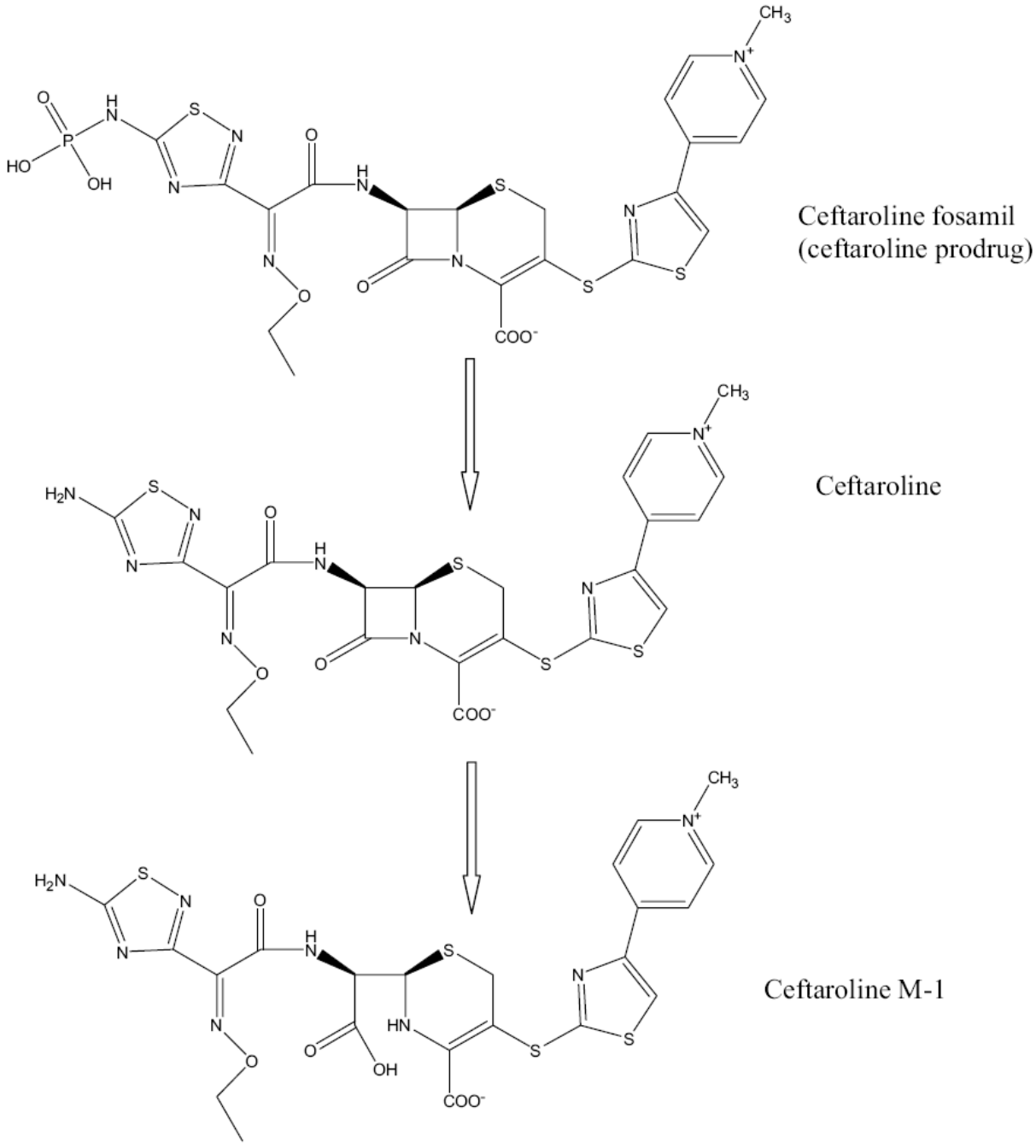
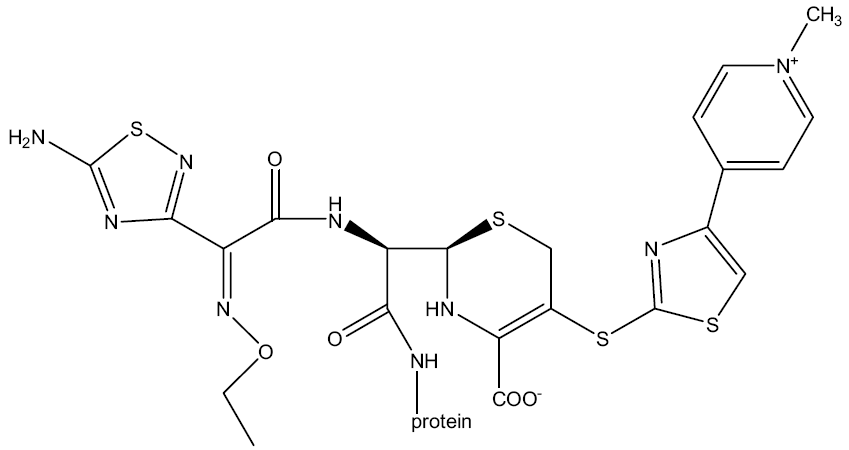


Figure 5. Proposed structure of ceftaroline-protein adduct



(ii) Urine: Ceftaroline (Peak 6) was also the major peak in the urine metabolite profile, with approximately 64.3% of the dose excreted as unchanged ceftaroline, followed by Peak 1 with 4.5% and ceftaroline M-1 (Peak 4) with 2.3%. Small amounts of Peak 2 (1.2%) and Peak 3 (0.76%) were observed in urine, and urine concentration of ceftaroline fosamil (Peak 5) was below the limit of detection (i.e., <450 cpm/200 μg/mL). Combined, these five peaks in urine contributed to approximately 72.4% of the dose versus approximately 84.7% for total radioactivity recovered in urine over 0-24 hour period, leaving approximately 12% of the dose unaccounted for.

Reviewer Comment: In earlier discussions with the Sponsor prior to NDA submission, the Sponsor attributed the unaccounted 12% of the dose to "background noise" or the compilation of small chromatographic peaks from bioanalytical analysis.

(iii) Feces: All four peaks (Peaks 1, 2, 3, and 6) in the feces metabolite profile contained only a small amount of the dose, each not exceeding an average of 2.1% of the dose; an average of 0.05% of the dose was excreted as unchanged ceftaroline (Peak 6) . Fecal concentration of Peak 4 and ceftaroline fosamil (Peak 5) was below the limit of detection (i.e., <450 cpm/200 μg/mL). Combined, these four peaks in feces contributed to approximately 3.29% of the dose versus approximately 5.57% for total radioactivity recovered in feces over 0-96 hour period.

Safety: Only one adverse event was reported; one episode of loss of appetite on Study Day 7, which was considered mild and possibly related to study drug. No clinically significant change in laboratory, vital signs, electrocardiogram, and physical exam findings was noted.

SPONSOR'S CONCLUSIONS: Following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg in healthy adult males (n=6):

- There were six chromatographic peaks detected in plasma, consisting of ceftaroline fosamil, ceftaroline, ceftaroline M-1 (by hydrolysis of the β-lactam ring of ceftaroline), and three unidentified minor metabolites.
- Approximately 87% of the radioactivity in the administered dose was excreted in urine (85% in urine within 24 hours) and approximately 6% of the dose was excreted in the feces.

- Urinary excretion was the principal route of elimination for ceftaroline and its metabolites; approximately 64.3% of the dose was excreted in urine as ceftaroline, 2.3% as M-1, and a combined 6.5% as the three minor unidentified metabolites.
- [^{14}C] ceftaroline fosamil was well-tolerated at the studied dose.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results. Results are consistent with pharmacokinetic data obtained from the single- and multiple-dose pharmacokinetic study, P903-01.

STUDY NO.: P903-14

A Phase 1, single-center, multiple-dose, open-label study to assess the effect of ceftaroline on the intestinal microflora of healthy human subjects

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Date(s): 2 Oct 2008 – 3 Dec 2008
Investigator(s): G Panagiotidis, MD
Clinical Site(s): Karolinska University Hospital, Stockholm, Sweden
Analytical Site(s): (b) (4)

OBJECTIVE:

- To assess the effect of ceftaroline on the intestinal microflora of healthy subjects
- To measure ceftaroline concentration in plasma and feces using bioassay techniques
- To describe the *in vitro* susceptibility of intestinal microflora to ceftaroline before, during, and after ceftaroline fosamil administration
- To determine the safety, tolerability, and pharmacokinetic profile of ceftaroline in healthy adult subjects

METHODS

Study Design: P90314 was a single-center, open-label, multiple-dose study in healthy adult subjects (n=12; 6 male, 6 female).

Inclusion Criteria: Males and females (using effective method of birth control); 18-45 years of age (inclusive); 18-30 kg/m^2 (inclusive) in body mass index (BMI); creatinine clearance (CrCL), as estimated with Cockcroft-Gault, >80 mL/min; and in good health as confirmed by medical history, physical exam, and laboratory evaluations were enrolled.

Treatment: Ceftaroline fosamil was administered as multiple 1-hour infusions of 600 mg IV Q12 on Days 1-7 for total of 13 doses. Powder containing ceftaroline fosamil and L-arginine (excipient) was reconstituted with Sterile Water for Injection, and then transferred into an infusion bag/bottle of 250 mL of 0.9% sodium chloride solution. The prepared infusion bag/bottle was stored at 2-8 ºC for no longer than 24 hours and used within 6 hours after preparation or after removal from refrigerated storage.

Any marketed or investigational systemic antimicrobials were prohibited from 90 days prior to first dose administration. Concomitant prescription or non-prescription medications (except for oral contraceptives and spermicide), including but not limited to herbal supplements, laxatives, and enemas, were prohibited from 14 days prior to the first dose.

Subjects were to refrain from drinking fluids during the AM infusion and for at least 1 hour after the end of study drug infusions on Study Days 2, 5, and 7. Subjects were required to abstain from alcohol- or grapefruit-containing products and from >3 servings/day of caffeine-containing products within 48 hours before the first dose.

Sample Collection: Plasma and fecal samples were collected (**Table 1**) and analyzed for pharmacokinetic and microbiological purposes.

Table 1. Sampling scheme for multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12 × 7 days

Pharmacokinetic	**Plasma** • Pre-dose on Day 1 • Pre-dose (within 15 min before start of infusion) and 60 min AFTER START of FIRST infusion of the day on Days 2 and 5 • Pre-dose (within 15 min before start of infusion) and 30, 60, 65, and 75 min, and 1.5, 2, 3, 6, 12, 24, and 48 h after START of FINAL infusion on Day 7 • Follow-Up (Day 14) and End-Of-Study (Day 21)
Microbiological	**Plasma (for bioassay)** • Day -1 • 60 min (within 5 min before end of infusion) AFTER START of FIRST infusion of the day on Days 2 and 5 • 60 min (within 5 min before end of infusion) and 48 h AFTER START of FINAL infusion on Day 7 • Follow-Up (Day 14) and End-Of-Study (Day 21) **Feces (for bioassay, culture, and susceptibility testing)** • Days -1, 2, 5, 7, 9, and at Follow-Up (Day 14) and End-Of-Study (Day 21)

Analytical Methods: Plasma pharmacokinetic samples were analyzed for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 by validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay (Method 3; PRD-RPT-BDM-00077, 2009) (**Table 2**).

Table 2. Bioanalytical results of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma

Criterion	Ceftaroline fosamil	Ceftaroline	Ceftaroline M-1	Comments
PLASMA				
Range	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	0.05-20 µg/mL (1:10 dilution tested with 16 µg/mL)	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	Satisfactory
LLOQ	0.05 µg/mL	0.05 µg/mL	0.05 µg/mL	Satisfactory
Linearity	R^2 ≥0.9954	R^2 ≥0.9977	R^2 ≥0.9871	Satisfactory
Accuracy	Within ±7.0%	Within ±5.3%	Within ±9.7%	Satisfactory
Precision	≤ 10.5%CV	≤9.5 %CV	≤10.7 %CV	Satisfactory
Stability	• Study Dates: 2 Oct 2008 – 3 Dec 2008 • Analysis Dates: 13 Apr – 22 Apr 2009 • Stability: 526 days at -70 ºC			Satisfactory

Microbiological Methods: Plasma samples were used as positive controls in bioassays of fecal samples for ceftaroline. Plasma concentrations of ceftaroline were determined in quadruplicate by bioassay using *Micrococcus luteus* ATCC 9341 as the test organism, with a lower limit of quantification of 0.25 mg/L. Best-fit standard curves were obtained by linear regression, and intra- and inter-assay precision were <10%.

Analysis of ceftaroline activity in feces was performed in duplicate using a bioassay. In brief, a disk containing fecal material was incubated in the center of an agar plate of the test organism *M. luteus* ATCC 9341, and ceftaroline concentration in the sample was determined by comparing the sample's zone of inhibition against those from fecal samples with known concentrations of

ceftaroline. Best-fit standard curves were obtained by linear regression, and intra- and inter-assay precision were <10%.

Aerobic and anaerobic bacteria in fecal samples were determined by culturing, isolating, and quantifying specific strains. The lower limit of detection was 10^2 colony-forming units (CFU)/gram. Change in log number of intestinal aerobic and anaerobic bacteria before and after study drug administration was calculated.

Ceftaroline susceptibility was tested on fecal samples from bacterial culture by using the agar dilution method. For purposes of this study, a provisional breakpoint of 4 mg/L for ceftaroline was used. The minimum inhibitory concentrations (MIC) for 50% and 90% of tested strains (MIC_{50} and MIC_{90}) were calculated.

Pharmacokinetic Assessment: Pharmacokinetic parameters for ceftaroline fosamil, ceftaroline, ceftaroline M-1 were determined using non-compartmental methods. Since doses were expressed in terms of anhydrous, acetate-free ceftaroline fosamil (MW, 684.68), corrections were made to the dose when calculating parameters for ceftaroline (MW, 604.70; 0.883 × ceftaroline fosamil dose) and ceftaroline M-1 (MW, 622.72; 0.909 × ceftaroline fosamil dose). Parameters included the following:

- C_{max}, maximum observed plasma concentration
- $AUC_{0\text{-}t}$, area under the curve up to time corresponding to the last measurable concentration
- $AUC_{0\text{-}\infty}$, area under the curve from time 0 to infinity
- T_{max}, corresponding time of C_{max}
- $t_{1/2}$, elimination half-life
- CL, plasma clearance
- V_{ss}, steady-state volume of distribution

RESULTS

Study Population: In total, 12 subjects were enrolled with an equal number of males and females. All subjects were white and mean age was 24.7 ± 5.9 years. Weight ranged 60.0-90.5 kg and BMI ranged 21.3-28.1 kg/m^2. Two female subjects were enrolled with baseline CrCL of 78.1 and 78.4 mL/min (due to error in Cockcroft-Gault calculation for female gender), despite the inclusion criteria of CrCL >80 mL/min. As such, CrCL of enrolled subjects ranged 78.1-121.8 mL/min.

Pharmacokinetics: Several protocol deviations with potential implications on pharmacokinetic results were identified (**Table 3**).

Plasma pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in healthy elderly and healthy young adult subjects are listed in **Table 4**. Mean estimates were similar to those from the single- and multiple-ascending dose study, P903-01, in which 6 healthy adults received multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12 for 14 days.

Table 3. Protocol deviations for multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12 for 7 days in healthy adults

Deviation	N	Comment
Dosing		
Full dose not received	1 occurrence in 1/12 subjects	Acceptable • Subject 4501-14001 received 552 mg instead of 600 mg for PM infusion on Day 3 • Deviation not anticipated to have significant impact
Infusion time >60 ± 10 min	1 occurrence each in 4/12 subjects	Acceptable • Occurred with intensive sampling in only 1 subject • Deviation not anticipated to have significant impact
Sampling – Plasma		
Missing sample / sampling time deviation	5 samples total from 4/12 subjects	Acceptable • Deviation not anticipated to have significant impact
Sampling – Feces		
Improper storage	2 samples total from 2/12 subjects	Acceptable • Only 1 sample analyzed and used after being left at room temperature for several hours • Deviation not anticipated to have significant impact

Table 4. Mean ± SD pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 following 1-hour IV infusions of ceftaroline fosamil 600 mg Q12 for 7 days in healthy adults

Parameter	Healthy Adults 600 mg Q12 × 7 days (n=12)
Ceftaroline fosamil	
C_{max} (µg/mL)	2.82 ± 0.74
T_{max} (h)[a]	0.63 (0.50-1.03)
$AUC_{0-\tau}$ (µg*h/mL)	2.21 ± 0.60
$t_{1/2}$ (h)	0.09 ± 0.03[b]
V_{ss} (L)	58.25 ± 14.38[b]
CL (L/h)	251.84 ± 45.17[b]
Ceftaroline	
C_{max} (µg/mL)	22.67 ± 3.67
T_{max} (h)[a]	1.03 (0.98-1.10)
$AUC_{0-\tau}$ (µg*h/mL)	61.33 ± 9.16
$t_{1/2}$ (h)	2.00 ± 0.21
V_{ss} (L)	19.54 ± 2.98
CL (L/h)	8.68 ± 1.33
Ceftaroline M-1	
C_{max} (µg/mL)	1.52 ± 0.29
T_{max} (h)[a]	2.41 (1.32-3.03)
$AUC_{0-\tau}$ (µg*h/mL)	12.27 ± 2.84
$t_{1/2}$ (h)	4.55 ± 0.30
V_{ss} (L)	243.62 ± 45.82
CL (L/h)	36.69 ± 7.83

[a] *Reported as median (minimum-maximum)*
[b] *Data from n=3*

Concentrations by Bioassay: Plasma concentrations of ceftaroline determined via bioassay methodology were similar to those by LC-MS/MS (**Table 5**). Ceftaroline was detectable in plasma during or immediately following the dosing period on Days 2, 5, and 7, but there were no measurable concentrations on Days -1, 9, 14, or 21.

Table 5. Ceftaroline plasma concentrations by LC-MS/MS versus bioassay methods

Subject	Ceftaroline Plasma Concentration (µg/mL)					
	Day 2		Day 5		Day 7	
	LC-MS/MS	Bioassay	LC-MS/MS	Bioassay	LC-MS/MS	Bioassay
4501-14001	22.2	26.2	18.8	25.2	17.8	29.8
4501-14002	20.2	28.3	19.9	19.7	18.0	18.0
4501-14003	18.1	17.5	19.0	20.5	17.7	22.7
4501-14004	27.4	29.3	24.4	33.2	25.9	26.4
4501-14005	23.6	26.2	24.7	23.8	20.8	20.4
4501-14006	28.7	34.8	27.2	28.3	25.5	25.2
4501-14007	22.3	17.7	25.2	23.0	23.1	18.9
4501-14008	24.6	25.3	24.9	22.3	22.4	24.3
4501-14009	21.8	25.5	20.9	20.0	20.6	25.2
4501-14010	23.4	22.7	25.5	25.9	22.8	21.6
4501-14011	27.5	26.4	29.4	24.4	26.9	25.7
4501-14012	28.3	31.0	23.3	27.6	25.1	27.0

In feces, there were no measurable concentrations of ceftaroline detected in any of the samples collected on Days -1, 2, 5, 7, 9, 14 or 21.

Effect on Intestinal Microflora: Bacterial counts in fecal samples (as CFU/g feces) during and following 7 days of ceftaroline fosamil 600 mg Q12 are displayed in **Figure 1** for aerobes and **Figure 2** for anaerobes.

For aerobic bacteria, counts of enterococci and *Candida albicans* were within normal variation. Median counts of *Escherichia coli* decreased by ~2.0 log CFU/g feces from baseline on Day 7 and by 1.5 log CFU/g feces on Day 9 with recovery to baseline numbers on Day 14; decrease was not considered microbiologically significant. Median counts of Enterobacteriaceae also did not change significantly from baseline through Day 14, although there were increased numbers of *Klebsiella pneumoniae* on Day 21 in one subject and *Citrobacter* spp. on Day 21 in five subjects.

For anaerobic bacteria, there were non-significant decreases of ~1.7 log CFU/g feces in lactobacilli and ~2.1 log CFU/g feces in bifidobacteria, as well as a non-significant increase of ~2.0 log CFU/g feces in *Clostridia* spp. during the 7 days of dosing, while median counts of *Bacteroides* were unaffected. Strains of *C. difficile* were isolated from two subjects on Days 5, 7, and 9, with cytotoxicity results were as follows:

- Subject 4501-14007: Day 5, Negative; Day 7, Positive; Day 9, Positive
- Subject 4501-14012: Day 5, Positive; Day 7, Positive; Day 9, Positive

All isolates were toxin B positive cytotoxin assay, and positive for ToxA and ToxB genes. No strains were positive for the binary toxin gene and no isolates belonged to any known international PCR-ribotype. No clinical symptoms were observed, and thus these findings were considered not clinically relevant.

Figure 1. Effect of ceftaroline on **aerobic intestinal microflora** following multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12 for 7 days in healthy adults

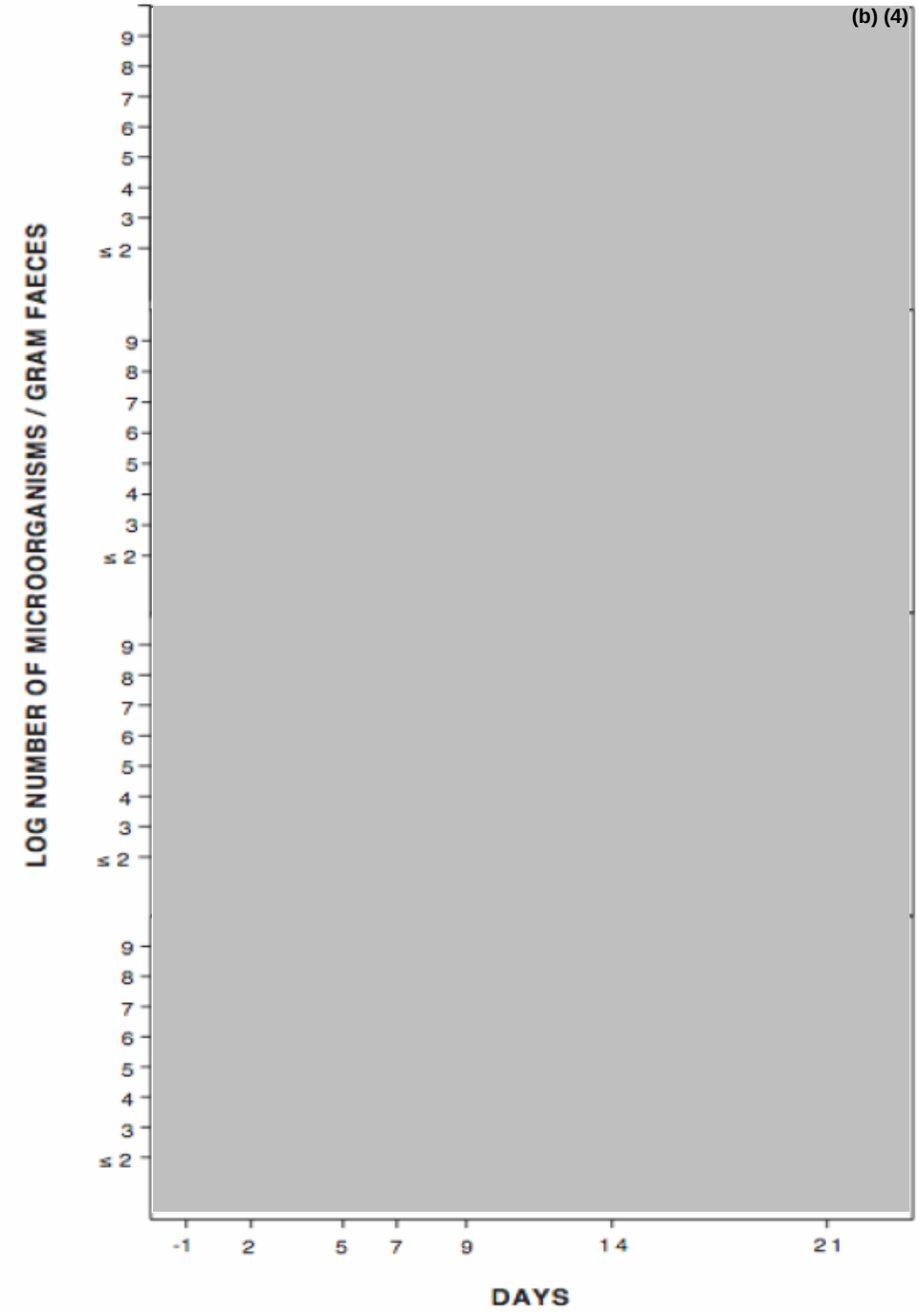
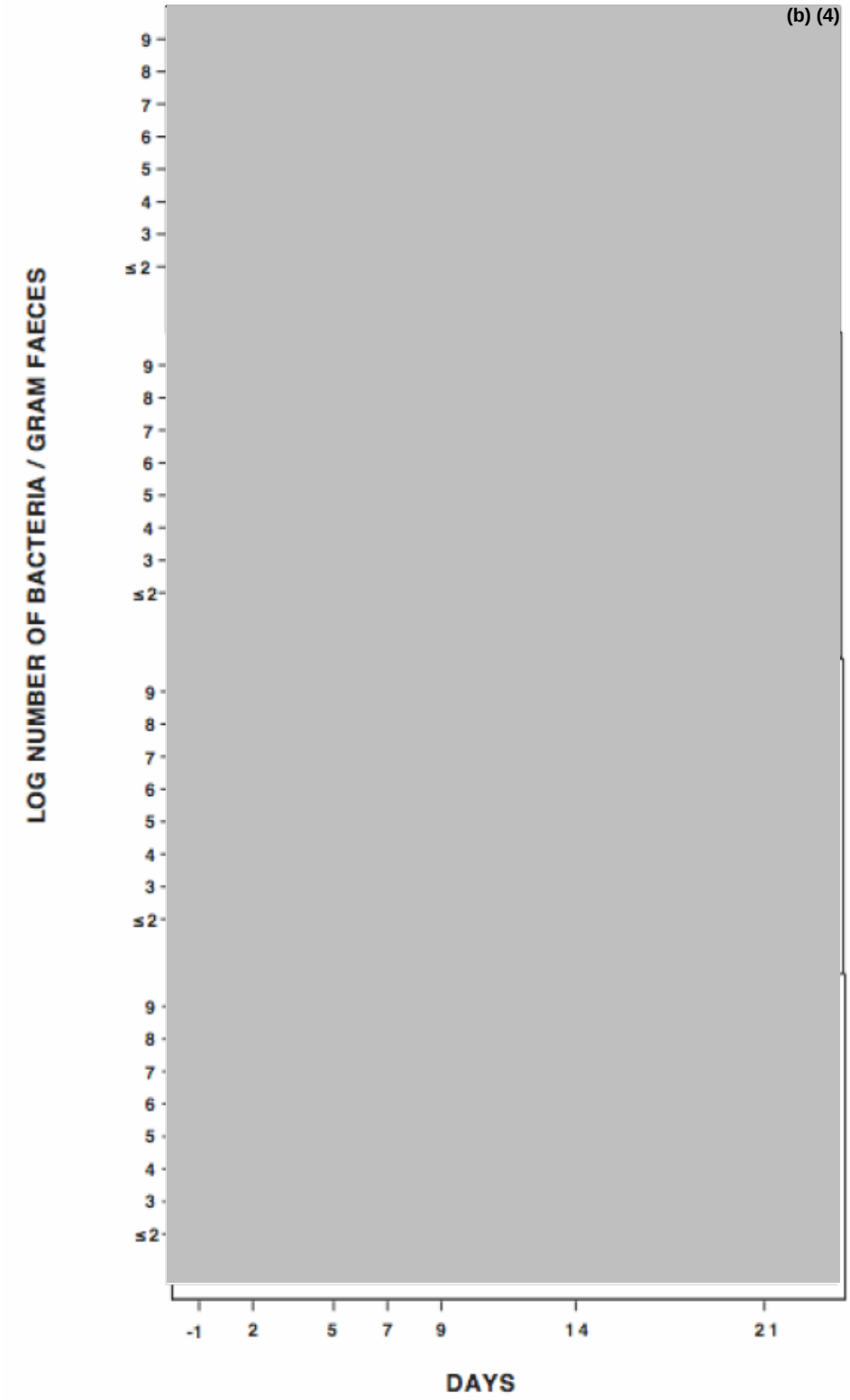


Figure 2. Effect of ceftaroline on **anaerobic intestinal microflora** following multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12 for 7 days in healthy adults



Susceptibility of Intestinal Microflora: No new colonizing aerobic or anaerobic bacteria with increased MICs (i.e., ≥4 mg/L) to ceftaroline were found. All *B. fragilis* strains (n=123) isolated were β-lactamase producers and thus, had elevated MICs (≥64 mg/L) as ceftaroline is inactive against β-lactamase-producing *Bacteroides* spp.

Reviewer Comment: Susceptibility results are limited with the agar dilution method, as MIC values were reported only in reference to the provisional breakpoint of 4 mg/L.

Safety: In total, 9 adverse events were reported by 5/12 (42%) subjects; all were considered mild in severity and resolved during the study. Of reported events, 6 were considered possibly or probably related to study drug and included nausea (n=2), diarrhea (n=1), stomach discomfort (n=1), vomiting (n=1), and rash (n=1).

Two subjects had low diastolic pressure on five occasions that were considered potentially clinically significant. Subject 4501-14003 had low diastolic pressure (44 or 47 mmHg vs 67 mmHg at baseline) pre-dose on Day 6, pre-dose and 1-hour post-dose on Day 7, and on Day 9. Subject 4501-14005 had low diastolic pressure (33 mmHg vs 50 mmHg at baseline) 1-hour post-dose on Day 3. However, none were associated with an adverse event and were not clinically significant.

Two subjects had electrocardiogram (ECG) values that were considered potentially clinically significant. Subject 4501-14004 had a low heart rate (46 bpm vs 60 bpm at baseline) 1 hour after start of infusion on Day 7. Subject 4501-14012 had a long QRS interval (105 msec vs 83 msec at baseline) 1 hour after start of infusion on Day 7 and a long QT interval (523 and 489 msec vs 438 msec at baseline) 1 hour after start of infusion on Day 7 and on Day 9. However, none of these subjects experienced an adverse event.

No clinically significant change (known to have clinical sequelae) in laboratory (chemistry, hematology, and urinalysis), vital signs, and ECG findings was noted.

SPONSOR'S CONCLUSIONS: Following multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12 for 7 days in healthy adult subjects:

- Ceftaroline plasma concentrations by bioassay showed activity during the drug administration period through Day 7 and no activity on Days 9, 14, and 21.
- No measurable fecal concentration of ceftaroline was found by bioassay at baseline or at any subsequent time point.
- Ceftaroline effects on aerobic intestinal microflora included no effect on the numbers of enterococci or *C. albicans*, no significant change in median counts of Enterobacteriaceae from baseline to Day 14, and a non-significant decrease in median counts of *E. coli* from baseline to Day 7 followed by recovery on Day 14.
- Ceftaroline effects on anaerobic intestinal microflora included non-significant decrease in the numbers of bifidobacteria and lactobacilli during the dosing period, non-significant increase in *Clostridia* spp. during dosing, and no effect on the numbers of *Bacteroides*.
- No new colonizing aerobic or anaerobic bacteria with ≥4-fold increased MIC to ceftaroline were found.

- Ceftaroline fosamil was well-tolerated in healthy adults for 7 days of multiple dose administration.
- Few adverse events were reported, all of which were mild; events considered possibly or probably related to study drug were mostly gastrointestinal in nature.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

4.1.3 Intrinsic Factors

APPEARS THIS WAY ON ORIGINAL

STUDY NO.: P903-02

An open-label pharmacokinetic, safety, and tolerability study of single intravenous doses of PPI-0903 in subjects with normal renal function, mild renal impairment, or moderate renal impairment

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Date(s): 11 Feb 2005 – 28 Feb 2006
Investigator(s)/Clinical Site(s): S Swan, MD; DaVita Clinical Research, Minneapolis, MN
T Marbury, MD; Orlando Clinical Research Center, Orlando, FL
Analytical Site(s): (b) (4)

OBJECTIVE:
- To evaluate the pharmacokinetics of single IV doses of PPI-0903 in subjects with normal renal function, mild renal impairment, and moderate renal impairment
- To evaluate the safety and tolerability of single IV doses of PPI-0903 in subjects with mild or moderate renal impairment

METHODS
Study Design: P903-02 was an open-label, single-dose study in subjects with normal renal function or mild or moderate renal impairment (n=18, total). Creatinine clearance (CrCL) was estimated with Cockcroft-Gault and subjects were enrolled into the following renal function cohorts:
- Normal renal function (n=6): CrCL >80 mL/min
- Mild renal impairment (n=6): CrCL >50 and ≤80 mL/min
- Moderate renal impairment (n=6): CrCL >30 and ≤50 mL/min

Inclusion Criteria: Males or females (using effective method of birth control) with normal renal function, or mild or moderate renal impairment (as defined by Cockcroft-Gault formula); 18-75 years of age (inclusive); and >18 kg/m^2 in body mass index (BMI) were enrolled.

Treatment: PPI-0903 was administered as a single 600 mg IV dose over 1-hour. PPI-0903 was reconstituted with 1.9% L-arginine in Water for Injection, and administered within 2 hours of reconstitution. (Earlier design of this study involved dosing PPI-0903 500 mg as a 0.5-hour IV infusion in subjects with normal renal function; data from this cohort will be disregarded for the purposes of this review.)

Probenecid was prohibited from 5 days prior to dosing until after 48-hour post dose sampling. For subjects with normal renal function, prescription and over-the-counter medications, including herbal supplements, were prohibited from 3 days prior to dosing, except for acetaminophen (allowed up to three 500 mg doses/day). For subjects with renal impairment, concomitant medications were allowed as medically necessary, provided the medication was not disallowed or used for an excluded medical condition. Permitted concomitant medications were

administered at least 2 hours before initiation of study drug infusion and/or at least 2 hours after completion of study drug infusion.

Subjects fasted from midnight on the night before the Study Day, and standardized meals, snacks, and beverages were provided during confinement. Subjects were to refrain from drinking fluids during study drug administration and for at least 1 hour after completion of study drug administration. Subjects were also required to abstain from alcohol and caffeine-containing food or drinks from 12 hours before until after the final sampling time point.

Sample Collection: Plasma and urine samples were collected (**Table 1**) and analyzed for pharmacokinetic purposes.

Table 1. Pharmacokinetic sampling scheme for single 1-hour IV infusion of PPI-0903 600 mg

Plasma	• Pre-dose • 20, 40, and 55 min AFTER START of infusion • 0.08, 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 36, and 48 h AFTER END of infusion • 60 and 72 h AFTER END of infusion (for moderate renal impairment only)
Urine	• 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, and 24-48 h AFTER START of infusion • 48-72 h AFTER START of infusion (for moderate renal impairment only)

Analytical Methods: Pharmacokinetic samples were analyzed for PPI-0903, PPI-0903M, and PPI-0903M-1 by validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) for plasma (Method 1; PRD-RPT-BDM-00128, 2004 and PRD-RPT-BDM-00131, 2007) and urine (Method 2; PRD-RPT-BDM-00129, 2004 and PRD-RPT-BDM-00127, 2007) (**Table 2**). All concentrations below the limit of quantification (BLQ) were excluded from pharmacokinetic analysis.

Table 2. Bioanalytical results of PPI-0903, PPI-0903M, PPI-0903M-1 in plasma and urine

Criterion	PPI-0903	PPI-0903M	PPI-0903M-1	Comments
PLASMA				
Range	0.010-2.0 µg/mL (1:10 & 1:100 dilution tested with 4.0 µg/mL)	0.010-2.0 µg/mL (1:10 & 1:100 dilution tested with 4.0 µg/mL)	0.010-2.0 µg/mL (1:10 & 1:100 dilution tested with 4.0 µg/mL)	Satisfactory
LLOQ	0.010 µg/mL	0.010 µg/mL	0.010 µg/mL	Satisfactory
Linearity	R^2 ≥0.9987	R^2 ≥0.9962	R^2 ≥0.9983	Satisfactory
Accuracy	Within ±8.7%	Within ±5.7%	Within ±7.9%	Satisfactory
Precision	≤13.5 %CV	≤12.9 %CV	≤9.2 %CV	Satisfactory
Stability	• Study Dates: 11 Feb 2005 – 28 Feb 2006 • Analysis Dates: 16 Mar 2005 – 16 Apr 2006 • Stability: 371 days at -70 ºC			Satisfactory
URINE				
Range	0.200-100.0 µg/mL (1:10 & 1:100 dilution tested with 200.0 µg/mL)	0.200-100.0 µg/mL (1:10 & 1:100 dilution tested with 200.0 µg/mL)	0.200-100.0 µg/mL (1:10 & 1:100 dilution tested with 200.0 µg/mL)	Satisfactory
LLOQ	0.200 µg/mL	0.200 µg/mL	0.200 µg/mL	Satisfactory
Linearity	R^2 ≥0.9991	R^2 ≥0.9987	R^2 ≥0.9995	Satisfactory
Accuracy	Within ±3.9%	Within ±4.0%	Within ±4.4%	Satisfactory
Precision	≤8.1 %CV	≤10.6 %CV	≤11.8 %CV	Satisfactory
Stability	• Study Dates: 11 Feb 2005 – 28 Feb 2006 • Analysis Dates: 16 Mar 2005 – 7 Apr 2006 • Stability: 520 days at -70 ºC			Satisfactory

Pharmacokinetic Assessment: Pharmacokinetic parameters for PPI-0903, PPI-0903M, and PPI-0903M-1 were determined using non-compartmental methods. Parameters included the following:

- C_{max}, peak observed plasma concentration
- AUC_t, area under the curve from time 0 to the last measured concentration
- AUC_{inf}, area under the curve from time 0 to infinity
- T_{max}, corresponding time of C_{max}
- $t_{1/2}$, elimination half-life
- CL, plasma clearance (adjusted for molecular weight for respective metabolite: PPI-0903M/PPI-0903 = 604.70/684.68 = 0.883; PPI-0903M-1/PPI-0903 = 622.72/684.68 = 0.909)
- CL_r, renal clearance
- % Urinary Recovery, percent of dose excreted in urine (adjusted for molecular weight for respective metabolite: PPI-0903M/PPI-0903 = 604.70/684.68 = 0.883; PPI-0903M-1/PPI-0903 = 622.72/684.68 = 0.909)
- V_{ss}, steady-state volume of distribution
- V_z, volume of distribution of terminal phase (adjusted for molecular weight for respective metabolite: PPI-0903M/PPI-0903 = 604.70/684.68 = 0.883; PPI-0903M-1/PPI-0903 = 622.72/684.68 = 0.909)

Concentrations occurring after C_{max} and after two or more consecutive BLQ results were excluded from pharmacokinetic analysis. Outlier concentrations (e.g., those that did not decrease in a manner consistent with the exponential decline of surrounding concentrations) were also excluded.

Statistical Methods: Geometric mean and geometric coefficient of variation (geometric %CV) were computed for pertinent pharmacokinetic parameters by renal function and dose.

RESULTS

Study Population: In total, 18 subjects were enrolled with an equal number of male and female subjects, and an equal number of black and white subjects. Mean ± SD age were 34.2 ± 8.3, 69.3 ± 5.8, and 49.0 ± 15.6 years for normal, mild, and moderate renal groups, respectively. Weights ranged 56.4-113.2 kg across renal cohorts, with 76.9 ± 9.2, 80.2 ± 12.8, and 85.7 ± 18.1 kg, for normal, mild, and moderate groups, respectively. BMI ranged 19.4-36.9 kg/m^2 across renal cohorts, with 26.3 ± 3.9, 28.0 ± 4.4, and 29.3 ± 4.5 kg/m^2 for normal, mild, and moderate groups, respectively. CrCL ranged 91.7-133.8 mL/min for the normal renal function group, 51.8-71.0 mL/min for the mild renal impairment group, and 30.1-42.5 mL/min for the moderate renal impairment group. Demographic characteristics (other than CrCL) were similar across renal cohorts except for age, with 5/6 subjects in the mild group >65 years old versus 0/6 subjects in the normal group and 1/6 subjects in the moderate group.

Pharmacokinetics: Several protocol deviations with potential implications on pharmacokinetic results were identified (**Table 3**).

Table 3. Protocol deviations for single 1-hour IV infusion of PPI-0903 in various renal function cohorts

Deviation	N	Comment
Dosing		
Infusion time deviation	1 occurrence each in 4/18 subjects (Mild, 1/6; Moderate, 3/6)	Acceptable • Deviated by ≤9 min; full doses were administered • Actual infusion times accounted for by actual sampling times
Sampling - Plasma		
Sampling time deviation	Many	Acceptable • Most deviated by ≤5 min; actual sampling times used in pharmacokinetic analysis
Sample not received	1 sample from 1/18 subjects	Acceptable • Missing result not anticipated to have significant impact: 01-352 (Moderate): Pre-dose
Sampling – Urine		
Sample not received	6	Acceptable • Results missing for following subjects: 02-151 (Normal): 0-2 h 02-153 (Normal): 0-2 h 02-252 (Mild): 0-2 h 01-353 (Moderate): 2-4, 6-8 h • Amount recovered in urine underestimated, however, exposures between renal groups based on plasma rather than urine
Bioanalytical - Plasma		
Missing results	1 sample from 1/18 subjects	Acceptable • Missing result not anticipated to have significant impact: 01-152 (Normal): 49 h (for PPI-0903M only)

Pharmacokinetic parameters of PPI-0903, PPI-0903M, and PPI-0903M-1 in subjects with normal renal function, and mild and moderate renal impairment are listed in **Table 4**. (Note: Estimates of V_{ss} were not provided for PPI-0903M or PPI-0903M-1 by the Sponsor.) Concentration-time profiles of PPI-0903M and PPI-0903M-1 are displayed in **Figure 1** and **Figure 2**, respectively.

Reviewer Comment: Plasma protein binding was not investigated in the different renal function groups, however, any changes in protein binding with renal impairment is unlikely to have a significant impact on the fraction unbound as ceftaroline is minimally bound to plasma proteins (~20%).

(i) PPI-0903 (prodrug): Exposures, C_{max} and AUC_{inf}, for prodrug PPI-0903 did not appear affected by renal function. T_{max} generally occurred within the 1-hour IV infusion, while $t_{1/2}$ was approximately ≤15 minutes across renal cohorts. Geometric mean V_{ss} and CL did not vary with renal impairment, ranging 28.3-32.5 L and 237.5-262.9 L/h, respectively, although high geometric %CV (i.e., >75%) was observed with V_{ss} in the mild and moderate groups due to a single outlier in each (large V_{ss} of 99.0 L in mild and small V_{ss} of 9.8 L in moderate). (Note: Due to rapid biotransformation of prodrug, pharmacokinetic parameters that involve proper characterization of the terminal phase were interpreted with caution.)

Unchanged PPI-0903 was not detected in urine, except for trace amounts in 5/6 subjects with moderate renal impairment, resulting in high geometric %CV (i.e., >75%) for CL_r (range, 0.00-0.47 L/h) and urinary recovery (range, 0.01-0.18%).

(ii) PPI-0903M (active metabolite): C_{max} for the active PPI-0903M did not appear to vary with renal function (**Figure 3**) and similarly T_{max} occurred around the end of 1-hour IV infusion regardless of the renal cohort. However, AUC_{inf} was greater in mild and more significantly so in moderate renal impairment versus those with normal renal function (**Figure 4**), with geometric means that were 19% and 52% greater, respectively. CL and CL_r expectedly decreased with decreasing renal function (as CrCL) (**Figure 5** and **Figure 6**, respectively), as did % urinary recovery; V_z appeared unchanged. Accordingly, geometric mean $t_{1/2}$ was extended in mild (3.61 hours) and moderate (4.49 hours) renal impairment versus normal renal function (2.84 hours) with corresponding slower elimination profiles. There were no pharmacokinetic parameters with geometric %CV >50%.

(iii) PPI-0903M-1 (inactive, open-ring metabolite of PPI-0903M): C_{max} and AUC_{inf} for major metabolite M-1 both increased with decreasing renal function (i.e., from normal function to mild and moderate impairment) (**Figure 7** and **Figure 8**, respectively). Geometric mean C_{max} was 26% and 88% greater, respectively, for mild and moderate impairment versus normal renal function. Exposure for M-1 was significantly impacted by renal impairment (more so than the active PPI-0903M), with geometric mean AUC_{inf} that was 67% greater for mild impairment, while the value for moderate renal impairment was 3.24 times that of normal renal function. Consequently, AUC_{inf} ratios to active PPI-0903M (calculated by the Reviewer) were greater for mild (0.31) and moderate (0.47) impairment versus normal renal function (0.22).

Similarly to PPI-0903M, CL and CL_r decreased with decreasing renal function (as CrCL) (**Figure 9** and **Figure 10**, respectively), as did % urinary recovery. Accordingly, geometric mean $t_{1/2}$ was extended in mild (6.39 hours) and moderate (9.26 hours) renal impairment versus normal renal function (5.68 hours) with corresponding slower elimination profiles. Unlike the active PPI-0903M, V_z also appeared to decrease with worsening renal function. For the moderately impaired group, geometric %CV for CLr and urinary recovery were >50% due to a single outlier with a higher % dose recovered in urine (7.13%).

T_{max} was variable for each renal cohort with geometric %CV >50%, and ranged 0.67-3.00, 0.92-5.00, and 2.00-9.00 hours for normal, mild, and moderate groups, respectively. This was largely due to the profile of declining M-1 concentrations (**Figure 11**), in which two peaks were observed. One peak occurred near the end of 1-hour IV infusion, as expected, for those with normal renal function, while a later peak occurred up to 4 and 8 hours following completion of infusion for those with mild and moderate impairment, respectively.

Reviewer Comment: Occurrence of this higher and delayed peak in M-1 concentrations for subjects with mild and moderate renal impairment can be theorized as attributable to a combination of the following: 1) greater circulating concentrations of the active PPI-0903M in mild and moderate renal impairment versus normal renal function, which translates to more PPI-0903M that is available for conversion/degradation into the open-ring metabolite, M-1, and

2) longer elimination $t_{1/2}$ of M-1 versus the active PPI-0903M that contributes to additional and delayed accumulation of M-1 concentrations.

Table 4. Geometric mean (geometric %CV) pharmacokinetic parameters of PPI-0903, PPI-0903M, and PPI-0903M-1 following single 1-hour IV infusion of PPI-0903 600 mg in subjects with normal renal function, and mild and moderate renal impairment

Parameter	Renal Function		
	Normal 600 mg (n=6)	Mild 600 mg (n=6)	Moderate 600 mg (n=6)
PPI-0903			
C_{max} (µg/mL)	3.56 (26.2)	3.80 (27.7)	3.26 (28.9)
T_{max} (h)	0.67 (0.0)	0.51 **(65.0)**	0.70 (48.2)
AUC_{inf} (µg*h/mL)	2.53 (29.4)	2.49 (29.0)	2.28 (12.1)
$t_{1/2}$ (h)	0.21 (39.7)	0.19 (49.8)	0.23 **(60.9)**
V_{ss} (L)	28.3 (43.8)	32.5 **(104.4)**	28.3 **(79.3)**
CL (L/h)	237.5 (29.4)	240.6 (29.0)	262.9 (12.1)
CL_r (L/h)	0.0 (0.0)	0.0 (0.0)	0.08 **(174.1)**
% Urinary Recovery	0.0 (0.0)	0.0 (0.0)	0.1 **(487.7)**
PPI-0903M			
C_{max} (µg/mL)	27.6 (29.0)	27.7 (22.7)	30.5 (17.5)
T_{max} (h)	0.97 (24.5)	0.99 (14.0)	1.12 (12.7)
AUC_{inf} (µg*h/mL)	75.1 (13.5)	89.4 (31.9)	114.1 (14.1)
$t_{1/2}$ (h)	2.84 (16.6)	3.61 (21.1)	4.49 (29.2)
V_z (L)	28.9 (19.4)	30.9 (46.1)	30.1 (20.4)
CL (L/h)	7.06 (13.5)	5.93 (31.9)	4.64 (14.1)
CL_r (L/h)	3.28 (27.0)	1.85 (19.6)	1.16 (33.4)
% Urinary Recovery	46.4 (13.7)	31.2 (32.8)	24.9 (34.4)
PPI-0903M-1			
C_{max} (µg/mL)	1.82 (29.8)	2.30 (37.3)	3.44 (19.2)
T_{max} (h)	1.15 **(71.1)**	1.90 **(123.1)**	5.70 **(81.1)**
AUC_{inf} (µg*h/mL)	16.6 (25.7)	27.7 (42.5)	53.8 (23.4)
$t_{1/2}$ (h)	5.68 (17.8)	6.39 (12.7)	9.26 (22.2)
V_z (L)	269.3 (16.7)	181.4 (41.3)	135.5 (24.2)
CL (L/h)	32.9 (25.7)	19.7 (42.5)	10.2 (23.4)
CL_r (L/h)	2.19 (33.7)	0.98 (30.7)	0.36 **(87.9)**
% Urinary Recovery	6.6 (22.6)	5.0 (23.9)	3.6 **(67.4)**

Bolded blue font indicates geometric %CV value **greater than 50%**
Bolded red font indicates geometric %CV value **greater than 75%**

Figure 1. Mean (standard error) **PPI-0903M** concentrations following single doses of PPI-0903 600 mg as a 1-hour IV infusion in subjects with normal renal function, and mild and moderate renal impairment

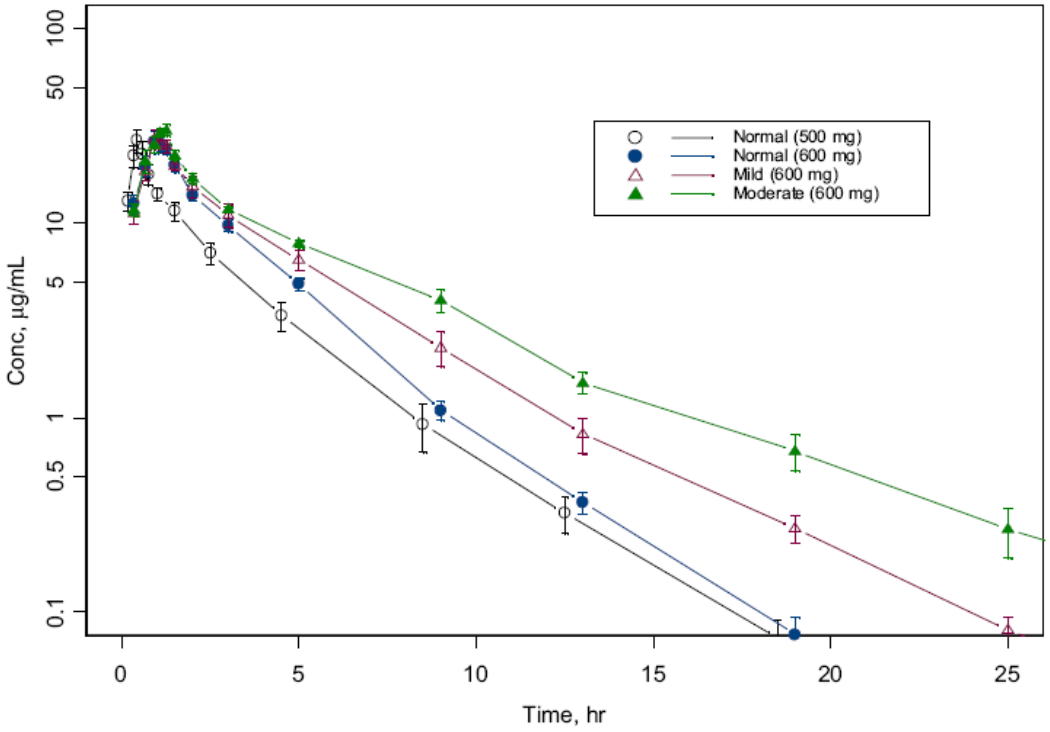


Figure 2. Mean (standard error) **PPI-0903M-1** concentrations following single doses of PPI-0903 600 mg as a 1-hour IV infusion in subjects with normal renal function, and mild and moderate renal impairment

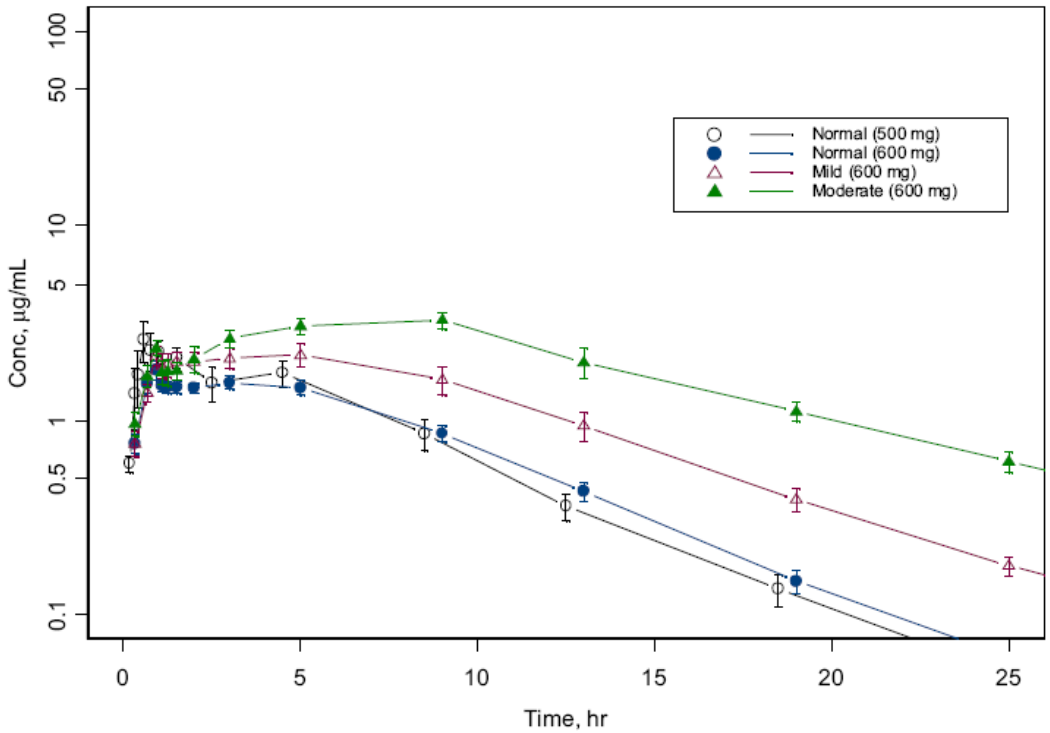


Figure 3. Individual **PPI-0903M C_{max}** in subjects with normal renal function, and mild and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

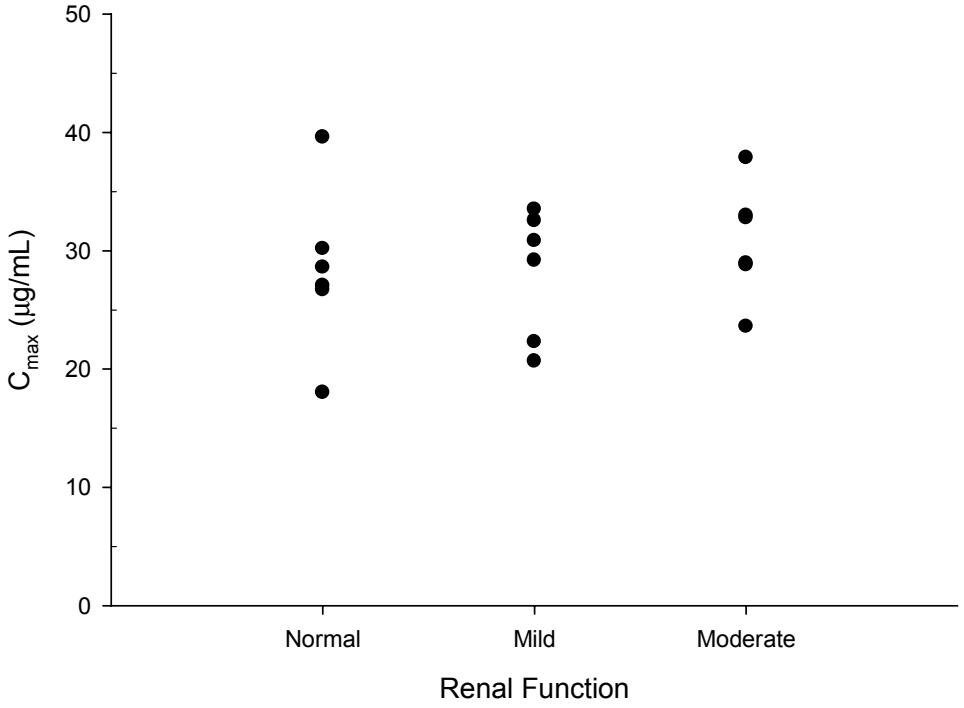


Figure 4. Individual **PPI-0903M AUC_{inf}** in subjects with normal renal function, and mild and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

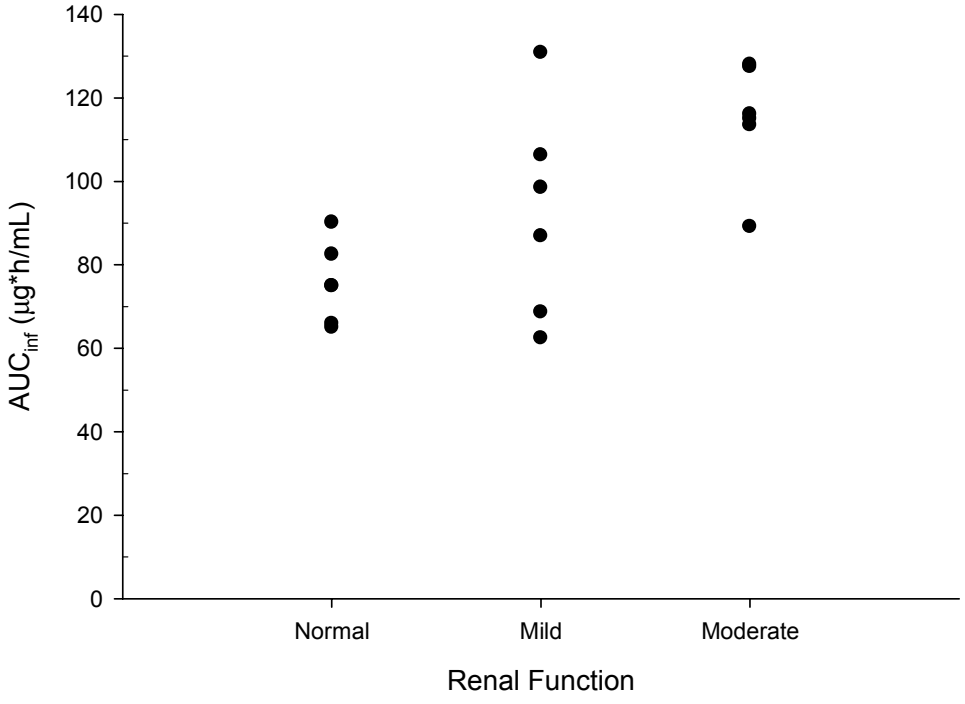


Figure 5. Relationship between **CrCL and PPI-0903M CL** in subjects with normal renal function, and mild and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

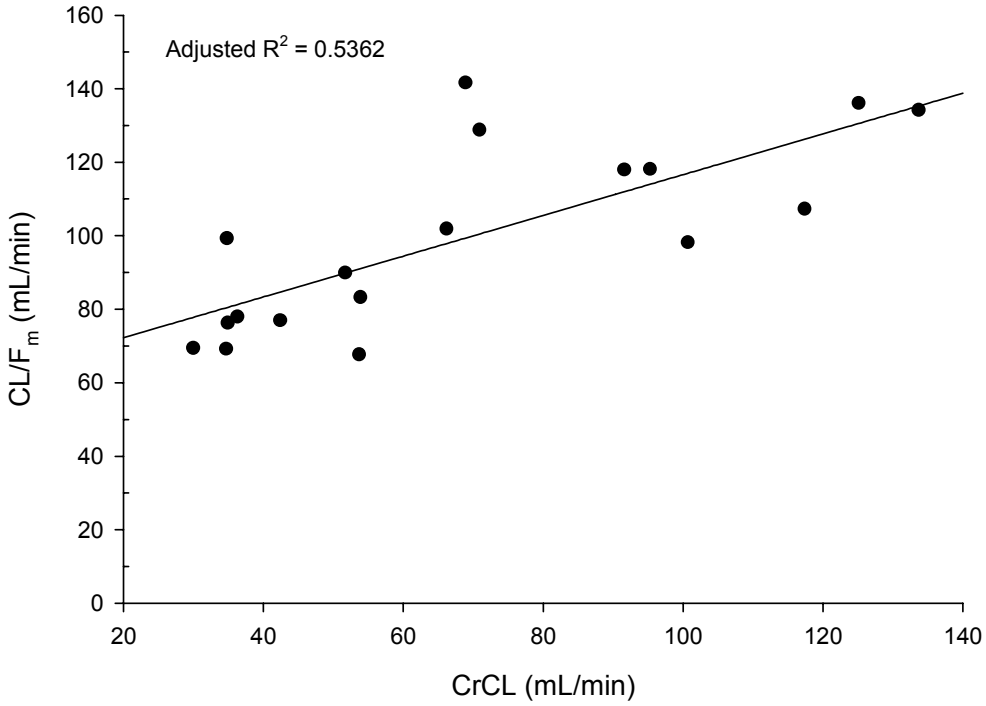


Figure 6. Relationship between **CrCL and PPI-0903M CL_r** in subjects with normal renal function, and mild and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

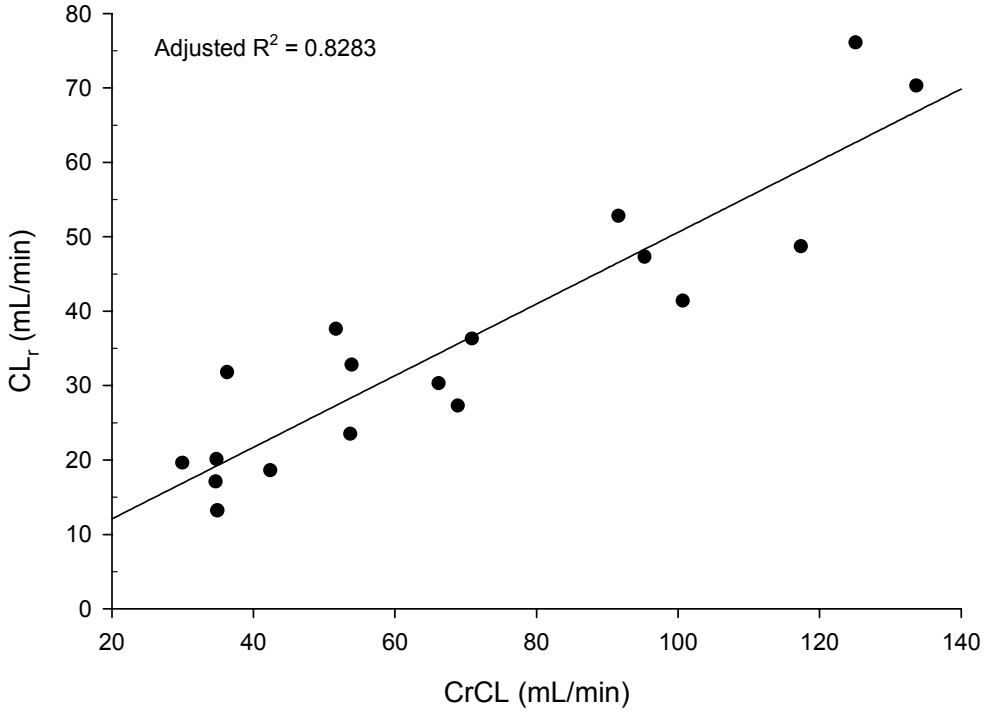


Figure 7. Individual **PPI-0903M-1 C_{max}** in subjects with normal renal function, and mild and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

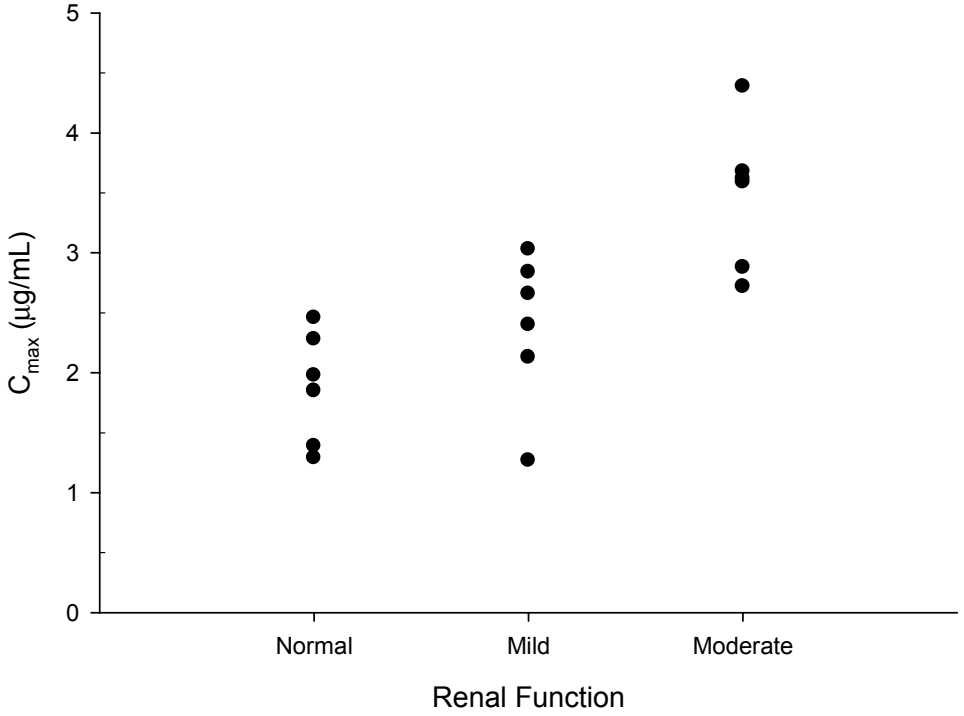


Figure 8. Individual **PPI-0903M-1 AUC_{inf}** in subjects with normal renal function, and mild and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

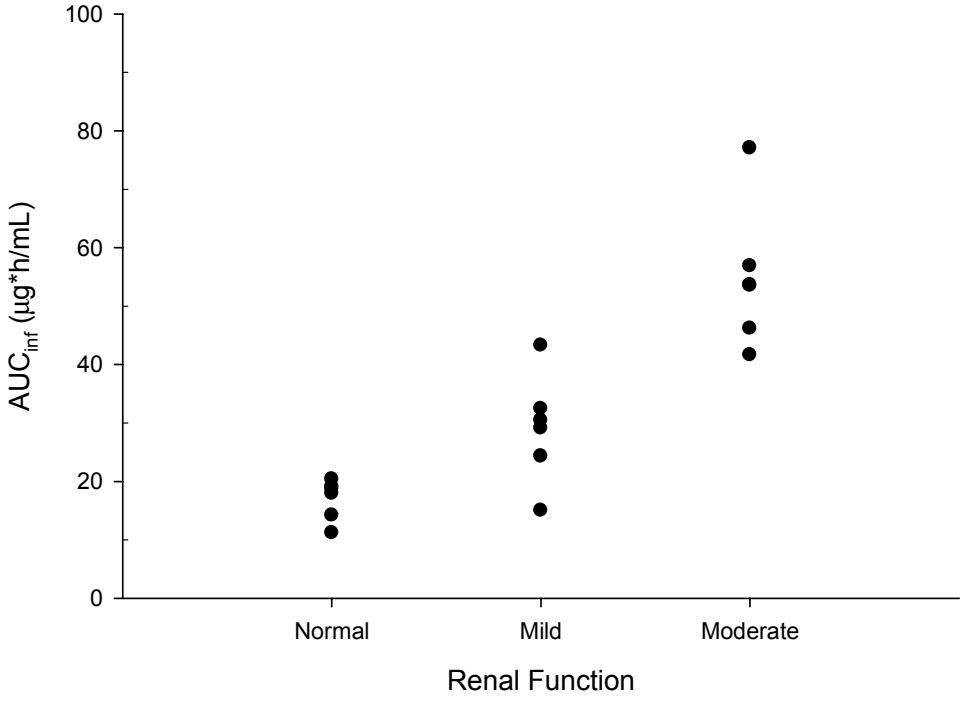


Figure 9. Relationship between **CrCL and PPI-0903M-1 CL** in subjects with normal renal function, and mild and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

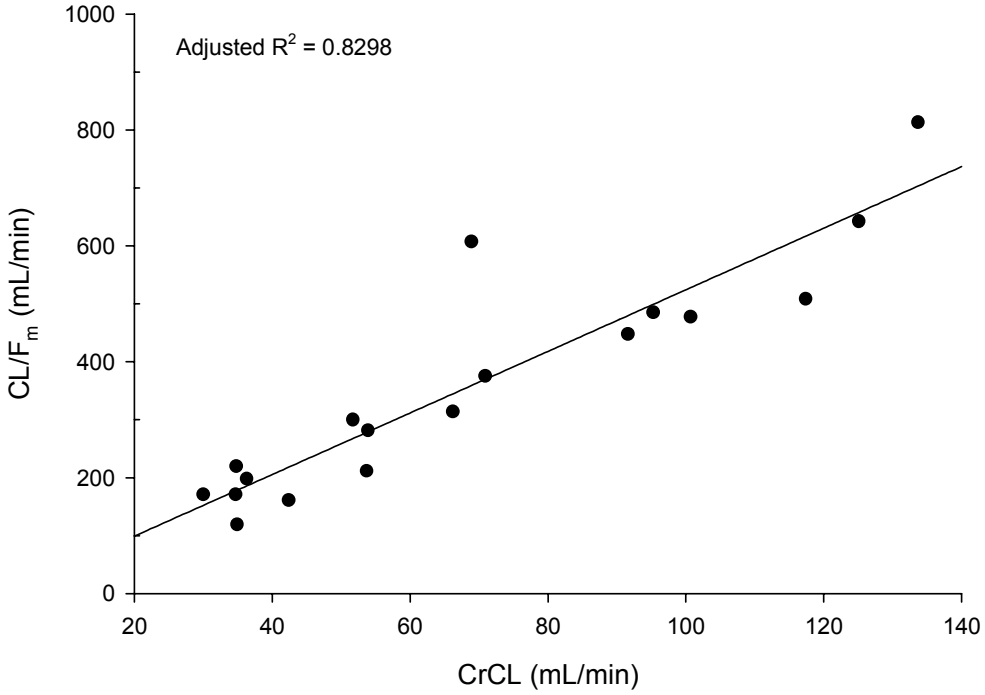


Figure 10. Relationship between **CrCL and PPI-0903M-1 CL_r** in subjects with normal renal function, and mild and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

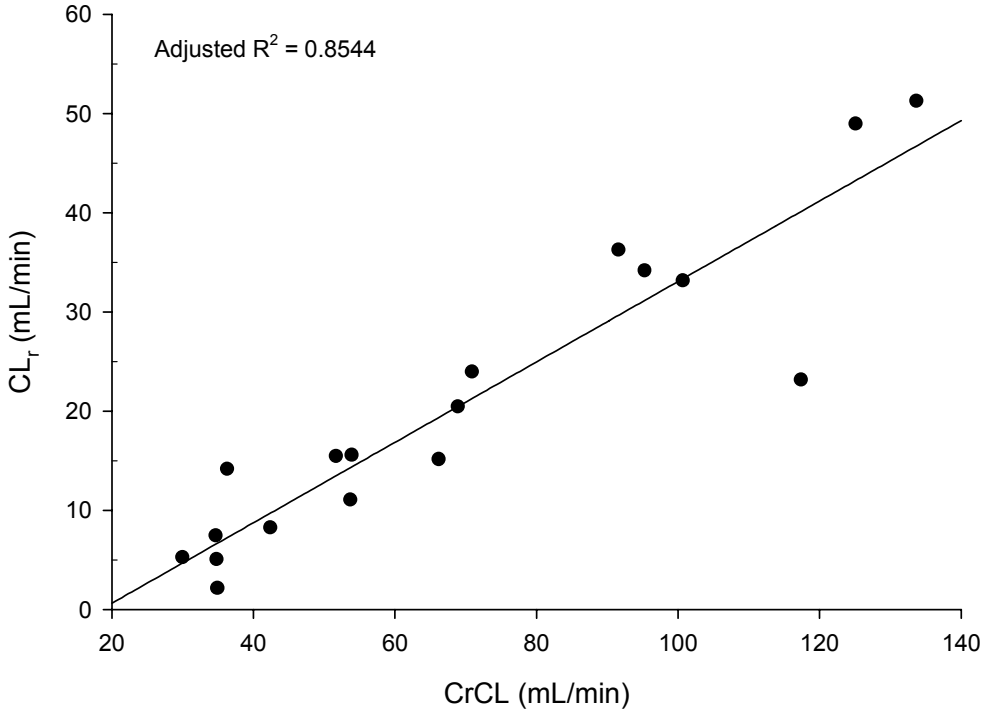
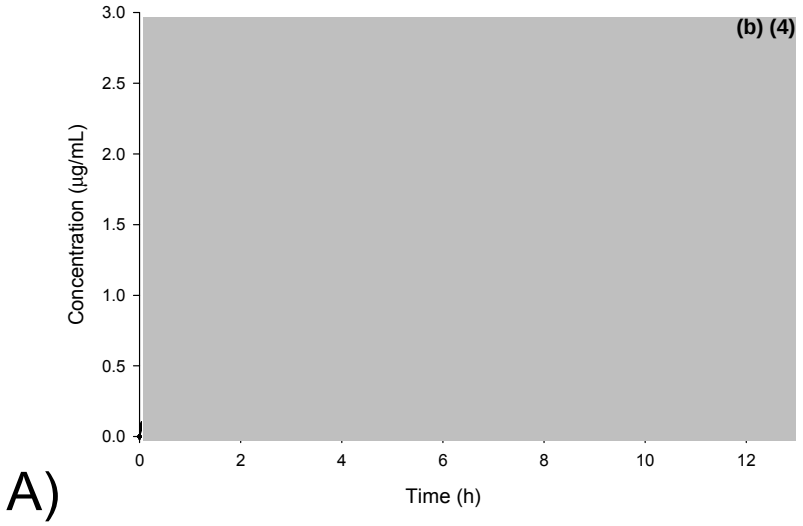
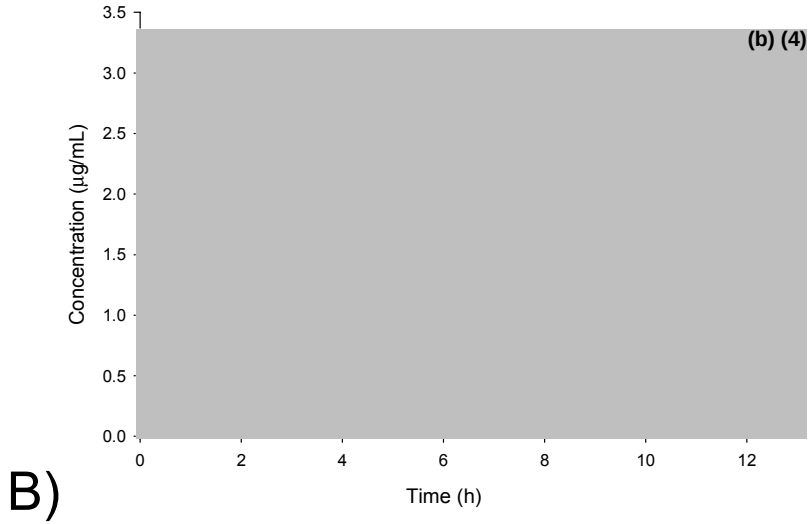
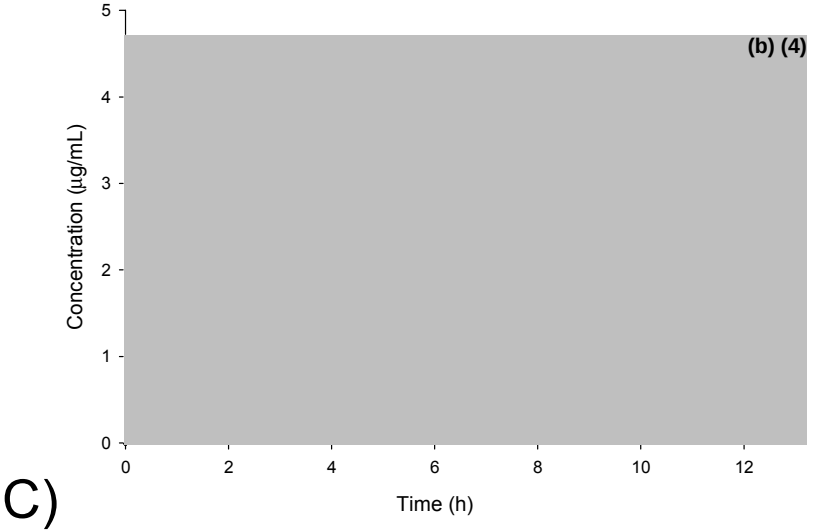


Figure 11. Individual **PPI-0903M-1** concentrations in subjects with **A)** normal renal function, and **B)** mild and **C)** moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg







Safety: In total, 25 adverse events were reported by 10/18 (56%) subjects and consisted of 11 events in 5/6 (83%) subjects with normal renal function, 5 events in 3/6 (50%) subjects with mild impairment, and 9 events in 2/6 (33%) subjects with moderate impairment. Of these, events considered possibly/probably related to study drug were reported in 5/18 (28%) subjects, with 2/6 (33%) subjects in the normal group, 3/6 (50%) subjects in the mild group, and 0/6 (0%) subjects in the moderate group; none were considered to be severe. Most commonly reported events were gastrointestinal (n=6; nausea, vomiting, diarrhea, and dry mouth) and nervous system (n=6; headache, dizziness, postural dizziness, and sinus headache) disorders by 6/18 (33%) subjects.

No clinically significant or serious abnormality in chemistry, hematology, and electrocardiogram findings was noted.

SPONSOR'S CONCLUSIONS: Following single 1-hour IV infusion of PPI-0903 600 mg in subjects with normal renal function (CrCL >80 mL/min), mild renal impairment (CrCL >50 and ≤80 mL/min), and moderate renal impairment (CrCL >30 and ≤50 mL/min):

- Pharmacokinetics of prodrug PPI-0903 did not differ for mild or moderate renal impairment versus normal renal function; PPI-0903 was rapidly converted into the active PPI-0903M regardless of renal function.
- Renal impairment had a notable impact on the pharmacokinetics of the active PPI-0903M and metabolite PPI-0903M-1; systemic exposure of PPI-0903M and PPI-0903M-1 were greater in subjects with mild and moderate renal impairment due to higher $t_{1/2}$, lower CL_r, and lower CL than in those with normal renal function.
- PPI-0903 was well-tolerated in subjects with normal renal function, mild renal impairment, or moderate renal impairment; most common adverse events were gastrointestinal and nervous system disorders.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results. Data from Study P903-02 was used in the development of final population pharmacokinetic models, which were then used to predict the probability of (pharmacokinetic/pharmacodynamic) target attainment to assess appropriateness of renal adjusted dosing (Reports ICPD 00174-8 and ICPD 00174-9). In the draft labeling, the Sponsor (b) (4) recommends 400 mg Q12 for moderate renal impairment (CrCL >30 and ≤50 mL/min).

The Reviewer performed additional pharmacokinetic analyses to verify the appropriateness of PPI-0903 400 mg Q12 for subjects with moderate renal impairment versus 600 mg Q12 for subjects with normal renal function using data from Study P903-02. Plasma concentration-time data of active PPI-0903M following single 1-hour IV infusions of PPI-0903 600 mg were fitted for each individual subject using WinNonlin software (version 5.2.1, Pharsight Corporation, Mountain View, CA). A two-compartment IV infusion model with microconstants, no lag time, first-order elimination, and 1/y*y weighting was used. The model was selected based on visual inspection of fit and goodness of fit measured by the Akaike Information Criterion (AIC) and weighted R^2.

The PPI-0903M-equivalent of the prodrug dose that was administered (0.883 × PPI-0903 dose, or 529.8 mg) and actual infusion times were used. Although numerous plasma samples deviated from scheduled times, since most deviated only by ≤5 minutes, scheduled time points were used and time points with zero concentration values after dose administration were omitted.

Once fitted, individual pharmacokinetic parameters were used to simulate PPI-0903 regimens in subjects with normal renal function (n=6) and moderate renal impairment (n=6) (**Table 5**). To check the accuracy of the 2-compartmental model, the Reviewer first simulated single 1-hour IV infusions of PPI-0903 600 mg (as done in Study P903-02), and compared simulated pharmacokinetic parameters of PPI-0903M against those reported using the Sponsor's non-compartmental analysis (**Table 6**). Simulated results by the Reviewer were found to be similar to reported results by the Sponsor.

Table 5. Median (min-max) estimates of PPI-0903M pharmacokinetic parameters used as input parameters for Reviewer simulations

Input Parameter	Normal Renal Function (n=6)	Moderate Renal Impairment (n=6)
V_1 (L)	14.92 (9.50-24.04)	15.60 (12.52-19.68)
k_{10} (1/h)	0.48 (0.31-0.86)	0.29 (0.23-0.47)
k_{12} (1/h)	0.10 (0.02-0.71)	0.15 (0.08-0.26)
k_{21} (1/h)	0.35 (0.16-0.74)	0.32 (0.21-0.46)

k_{10}, elimination rate constant; k_{12} and k_{21}, microtransfer rate constants between central and 2nd compartments; V_1, apparent volume of distribution of central compartment

Table 6. PPI-0903M pharmacokinetic parameters by Sponsor's non-compartmental analysis versus Reviewer's 2-compartmental analysis for subjects with normal renal function and moderate renal impairment following single 1-hour IV infusions of PPI-0903 600 mg

Normal Renal Function						
Subject No.	01-151	01-152	01-153	02-151	02-152	02-153
C_{max} (µg/mL)						
Sponsor	26.69	27.04	39.61	28.59	18.01	30.17
Reviewer	22.21	30.13	36.60	27.89	18.86	27.09
AUC_{inf} (µg*h/mL)						
Sponsor	64.98	65.91	90.15	74.91	74.94	82.49
Reviewer	64.39	64.71	84.95	72.99	72.15	80.50
$t_{1/2}$ (h)						
Sponsor	3.07	2.26	2.70	2.56	3.40	3.20
Reviewer	3.21	2.15	2.45	2.54	4.67	3.88
Moderate Renal Impairment						
Subject No.	01-351	01-352	01-353	01-354	02-351	02-352
C_{max} (µg/mL)						
Sponsor	32.78	32.97	37.87	28.94	28.79	23.60
Reviewer	30.55	32.57	31.71	24.78	23.70	23.07
AUC_{inf} (µg*h/mL)						
Sponsor	89.16	116.05	127.43	114.99	127.95	113.45
Reviewer	90.12	111.06	124.29	114.22	121.93	111.79
$t_{1/2}$ (h)						
Sponsor	3.02	3.72	4.33	5.58	5.83	5.14
Reviewer	3.11	3.48	3.95	5.14	6.16	5.14

Accuracy of the 2-compartmental model confirmed, the Reviewer then simulated steady-state exposures of active PPI-0903M for the standard PPI-0903 regimen (600 mg Q12 × 3 days) in subjects with normal renal function and the renal-adjusted regimen (400 mg Q12 × 3 days) in those with moderate renal impairment. For Reviewer simulations, the PPI-0903M-equivalent of the prodrug dose (0.883 × PPI-0903 dose) was used and all doses were 1-hour IV infusions. Calculation of %*f*T>MIC (target pharmacokinetic/pharmacodynamic parameter) assumed equal protein binding between renal groups (20%) and was determined in 0.2-hour increments over the dosing interval.

Reviewer-simulated profiles of active PPI-0903M following PPI-0903 600 mg Q12 × 3 days in subjects with normal renal function and PPI-0903 400 mg Q12 × 3 days in those with moderate renal impairment are shown in **Figure 12**. Geometric mean of simulated C_{max} in the moderate group (19.69 µg/mL) was only 27% lower than the normal group (26.94 µg/mL) (**Figure 13**), while similar between renal groups for AUC_{12} (normal, 72.90 µg*h/mL; moderate, 74.43 µg*h/mL) at their respective doses (**Figure 14**). Moreover, individual %*f*T>MIC curves over theoretical bacterial MICs for the adjusted 400 mg Q12 regimen in those with moderate renal impairment were comparable to or greater than that of the standard 600 mg Q12 regimen in subjects with normal renal function (**Figure 15**).

Based on Study P903-02 data, the renal-adjusted PPI-0903 regimen of 400 mg Q12 appears to be appropriate for subjects with moderate renal impairment (CrCL >30 and ≤50 mL/min) in matching active PPI-0903M exposures (as AUC and %*f*T>MIC) of the standard 600 mg Q12 regimen in subjects with normal renal function (CrCL >80 mL/min).

Figure 12. Individual **PPI-0903M concentrations at steady-state** in subjects with normal renal function and moderate renal impairment, **simulated by the Reviewer**

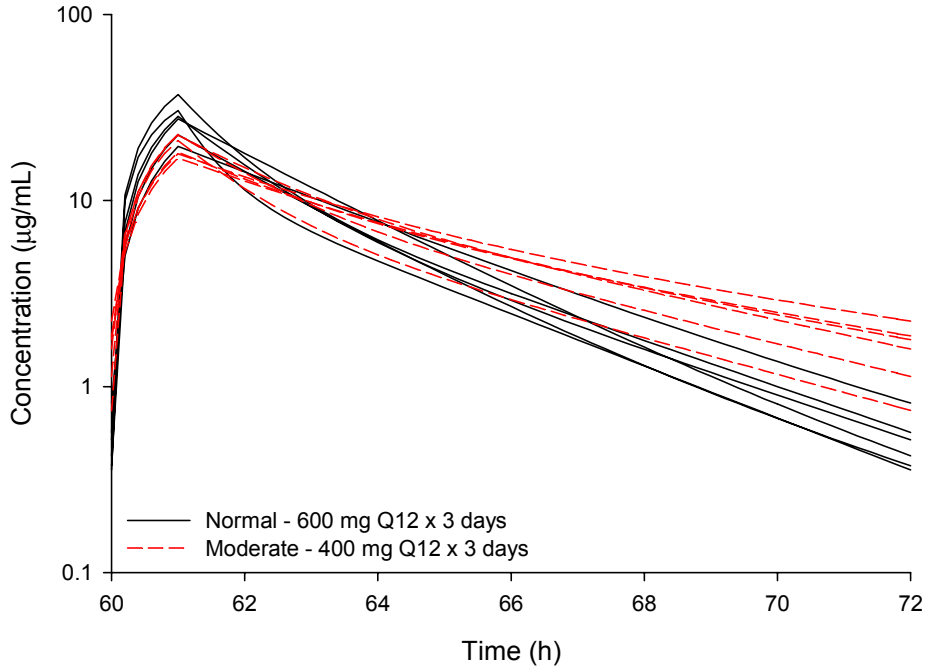
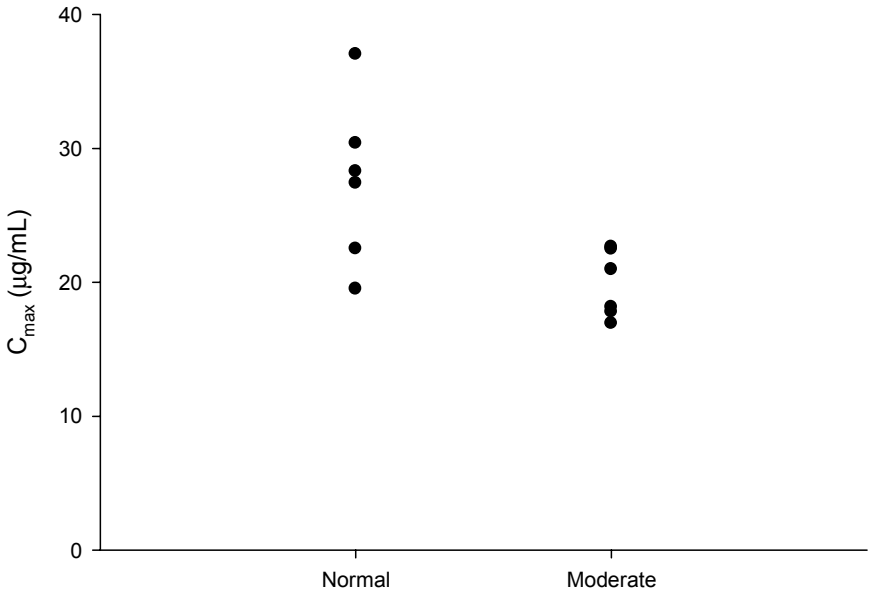
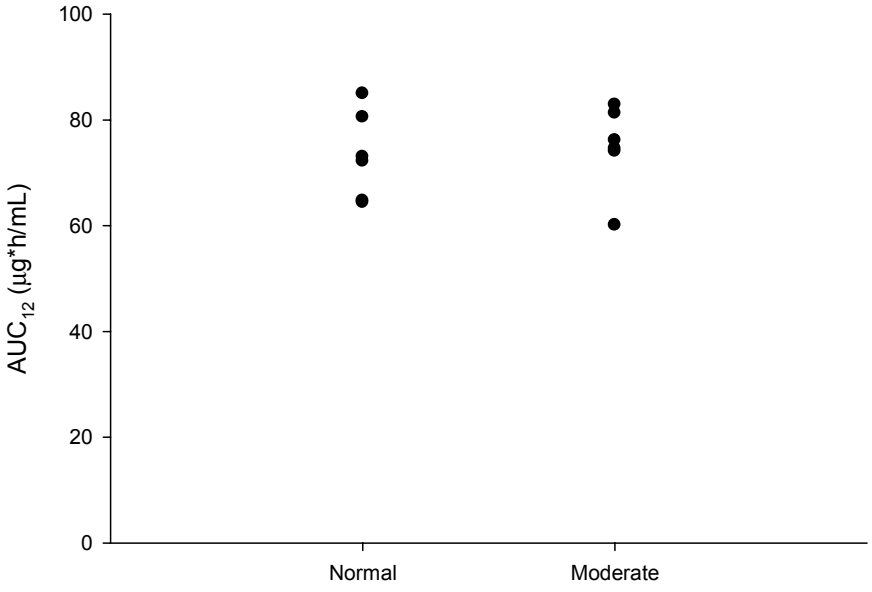


Figure 13. Individual **PPI-0903M C_{max} at steady-state** in subjects with normal renal function and moderate renal impairment, **simulated by the Reviewer**



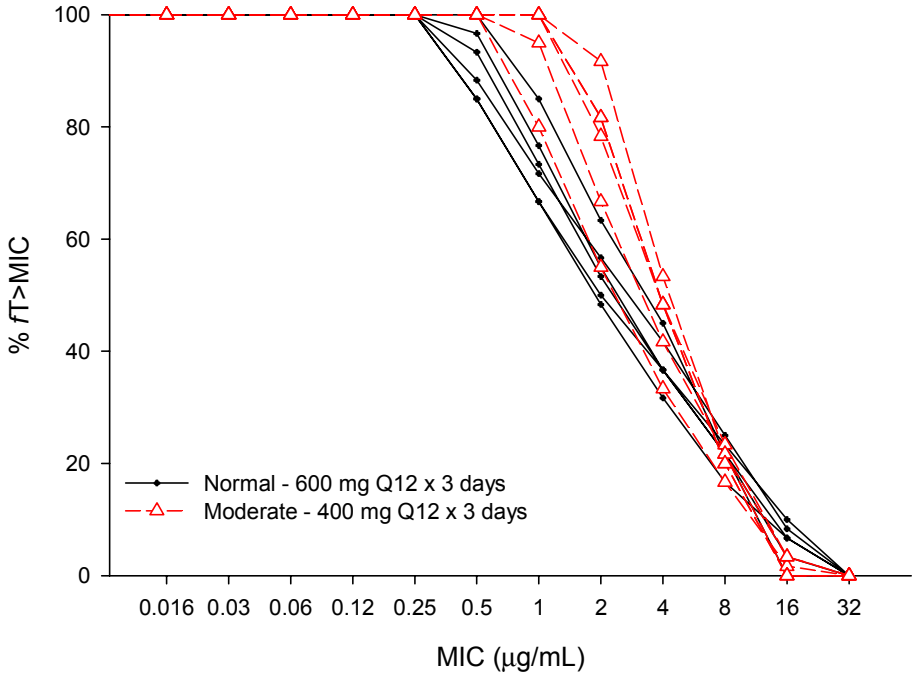
Normal - 600 mg Q12 x 3 days
Moderate - 400 mg Q12 x 3 days

Figure 14. Individual **PPI-0903M AUC_{12} at steady-state** in subjects with normal renal function and moderate renal impairment, **simulated by the Reviewer**



Normal - 600 mg Q12 x 3 days
Moderate - 400 mg Q12 x 3 days

Figure 15. Individual **PPI-0903M % *f*T>MIC at steady-state** in subjects with normal renal function and moderate renal impairment, **simulated by the Reviewer**



STUDY NO.: P903-04

An open-label pharmacokinetic, safety, and tolerability study of single intravenous doses of ceftaroline in subjects with normal renal function or severe renal impairment

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Date(s): 28 Apr 2007 – 6 Jun 2008
Investigator(s)/Clinical Site(s): T Marbury, MD; Orlando Clinical Research Center, Orlando, FL
JL Ruckle, MD/T Murtaugh, MD; Covance Clinical Research Unit, Honolulu, Hawaii
AB Vuitkullird, DO; West Coast Clinical Trials, Cypress, CA
Analytical Site(s): (b) (4)

OBJECTIVE:
- To evaluate the pharmacokinetic profile of a single IV dose of ceftaroline fosamil in subjects with normal renal function or severe renal impairment
- To evaluate the safety and tolerability of a single IV dose of ceftaroline fosamil in subjects with normal renal function or severe renal impairment

METHODS
Study Design: 903-04 was an open-label, single-dose study in subjects with normal renal function or severe renal impairment (n=12, total). Creatinine clearance (CrCL) was estimated with Cockcroft-Gault and subjects were enrolled into the following renal function cohorts:
- Normal renal function (n=6): CrCL >80 mL/min
- Severe renal impairment (n=6): CrCL ≤30 mL/min

Inclusion Criteria: Males or females (using effective method of birth control) with normal renal function or severe renal impairment (as defined by Cockcroft-Gault formula), ≥18 years of age, and >18 kg/m^2 in body mass index (BMI) were enrolled. Subjects in the normal renal function group were individually matched to subjects with severe renal impairment for age (±10 years), gender, and weight (±20%).

Treatment: Ceftaroline fosamil was administered as a single 400 mg IV dose over 1 hour. Powder containing ceftaroline fosamil and L-arginine (excipient) was reconstituted with Sterile Water for Injection, and then transferred into an infusion bag/bottle of 250 mL of 0.9% sodium chloride solution. The prepared infusion bag/bottle was stored at 2-8 ºC for no longer than 24 hours and used within 6 hours after being removed from refrigerated storage.

Probenecid was prohibited from 5 days prior to dosing until after 48-hour post dose sampling. For subjects with normal renal function, prescription and over-the-counter medications, including herbal supplements, were prohibited from 7 days prior to dosing. For subjects with renal impairment, concomitant medications were allowed, provided the medication did not conflict with other inclusion/exclusion criteria.

Subjects fasted from midnight on the night before the Study Day, and standardized meals, snacks, and beverages were provided during confinement. Subjects were to refrain from drinking fluids during study drug administration and for at least 1 hour after completion of study drug administration. Subjects were also required to abstain from alcohol and caffeine-containing food or drinks from 12 hours before until after the final sampling time point.

Sample Collection: Plasma and urine samples were collected (**Table 1**) and analyzed for pharmacokinetic purposes.

Table 1. Pharmacokinetic sampling scheme for single 1-hour IV infusion of ceftaroline fosamil 400 mg

Plasma	• Pre-dose • 20, 40, and 55 min AFTER START of infusion • 0.08, 0.25, 0.5, 1, 2, 4, 8, 12, 18, 24, 36, and 48 h AFTER END of infusion • 60 and 72 h AFTER END of infusion (for severe renal impairment only)
Urine	• Pre-dose • 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, and 24-48 h AFTER START of infusion • 48-72 h AFTER START of infusion (for severe renal impairment only)

Analytical Methods: Pharmacokinetic samples were analyzed for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 by validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays for plasma (Method 3; PRD-RPT-BDM-00077, 2009) and urine (Method 4; PRD-RPT-BDM-00080, 2008) (**Table 2**). Plasma concentrations below the limit of quantification (BLQ) were treated as zero for pharmacokinetic analysis.

Table 2. Bioanalytical results of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma and urine

Criterion	Ceftaroline fosamil	Ceftaroline	Ceftaroline M-1	Comments
PLASMA				
Range	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	0.05-20 µg/mL (1:10 dilution tested with 16 µg/mL)	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	Satisfactory
LLOQ	0.05 µg/mL	0.05 µg/mL	0.05 µg/mL	Satisfactory
Linearity	R^2 ≥0.9906	R^2 ≥0.9903	R^2 ≥0.9886	Satisfactory
Accuracy	Within ±4.9%	Within ±5.1%	Within ±6.0%	Satisfactory
Precision	≤7.8 %CV	≤10.4 %CV	≤8.8 %CV	Satisfactory
Stability	• Study Dates: 28 Apr 2007 – 6 Jun 2008 • Analysis Dates: 14 May 2008 – 17 Jul 2008 • Stability: 526 days at -70 ºC			Satisfactory
URINE				
Range	0.5-5 µg/mL (1:5 dilution tested with 3.8 µg/mL)	0.5-50 µg/mL (1:9 dilution tested with 38 µg/mL)[a]	0.5-50 µg/mL (1:5 dilution tested with 38 µg/mL)	Satisfactory
LLOQ	0.5 µg/mL	0.5 µg/mL	0.5 µg/mL	Satisfactory
Linearity	R^2 = 0.9843	R^2 ≥0.9944	R^2 ≥0.9900	Satisfactory
Accuracy	Within ±6.0%	Within ±8.0%	Within ±7.3%	Satisfactory
Precision	≤6.4 %CV	≤11.0 %CV	≤7.5 %CV	Satisfactory
Stability	• Study Dates: 28 Apr 2007 – 6 Jun 2008 • Analysis Dates: 22 May 2008 – 14 Jul 2008 • Stability: 469 days at -70 ºC			Satisfactory

[a] *Dilution integrity was evaluated further for ceftaroline in urine during analysis for Study P903-04*

Pharmacokinetic Assessment: Pharmacokinetic parameters for ceftaroline fosamil, ceftaroline, ceftaroline M-1 were determined using non-compartmental methods. Since doses were expressed in terms of anhydrous, acetate-free ceftaroline fosamil (MW, 684.68), corrections were made to the dose when calculating parameters for ceftaroline (MW, 604.70; 0.883 × ceftaroline fosamil dose) and ceftaroline M-1 (MW, 622.72; 0.909 × ceftaroline fosamil dose). Parameters included the following:

- C_{max}, maximum observed plasma concentration
- AUC_{0-t}, area under the curve up to time corresponding to the last measurable concentration
- $AUC_{0-\infty}$, area under the curve from time 0 to infinity
- T_{max}, corresponding time of C_{max}
- $t_{1/2}$, elimination half-life
- CL, plasma clearance
- V_{ss}, steady-state volume of distribution
- Ae_{0-t}, cumulative amount of drug excreted during entire urine collection period from time 0 to time t
- CL_r, renal clearance

Statistical Methods: Pharmacokinetic parameters for subjects with normal renal function and severe renal impairment were compared using Statistical Analysis System (SAS) Version 9.1.3. The paired difference between each subject with severe renal impairment and the matched subject with normal renal function in log-transformed C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, CL, Ae_{0-t}, and CL_r was analyzed using the one-sample t-test, while T_{max} was analyzed using the Wilcoxon Signed-Rank test. The 90% confidence interval (CI) was constructed for the geometric mean ratio for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, CL, Ae_{0-t}, and CL_r between impaired subjects and matched normal subjects. The relationships between pharmacokinetic parameter estimates and CrCL were investigated using simple linear regression analysis.

RESULTS

Study Population: In total, 12 subjects were enrolled, and subjects with normal renal function were well matched to those with severe renal impairment by age, gender, and weight as intended. Mean ± SD age was 63.5 ± 9.1 and 65.2 ± 8.4 years, respectively, for normal and severe renal groups. All study subjects were male, except for 1 female in each renal cohort. Subjects in the normal group were all white, while the renally impaired group consisted of 2/6 White, 2/6 Black, and 2/6 Asian/Pacific Islander. Weight ranged 63.5-114.8 kg across renal cohorts, with 88.4 ± 12.8 and 84.8 ± 19.1 kg for normal and severe groups, respectively. BMI ranged 23.5-36.3 kg/m^2 across renal cohorts, with 27.4 ± 2.8 and 29.9 ± 4.2 kg/m^2 for normal and severe groups, respectively. CrCL ranged 80.2-139 mL/min for the normal renal function group and 15-30 mL/min for the severe renal impairment group.

Pharmacokinetics: Pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in subjects with normal renal function and severe renal impairment are listed in **Table 3**. Concentration-time profiles of ceftaroline and ceftaroline M-1 are displayed in **Figures 1** and **2**, respectively. There were no pharmacokinetic parameters with coefficient of variation (%CV) >50% except for ceftaroline fosamil due to its rapid bioconversion to active ceftaroline, making determination of certain parameters difficult.

Reviewer Comment: Plasma protein binding was not investigated in the different renal function groups, however, any changes in protein binding with renal impairment is unlikely to have a significant impact on the fraction unbound as ceftaroline is minimally bound to plasma proteins (~20%).

(i) Ceftaroline fosamil (prodrug): Unlike mild and moderate renal impairment (from Study P903-02), both C_{max} and AUC_{0-t} were significantly greater in subjects with severe renal impairment than in those with normal renal function at the same dose, with geometric mean ratios of 1.65 and 2.04, respectively. T_{max} expectedly occurred during the 1-hour IV infusion regardless of the renal cohort, due to rapid conversion to the active ceftaroline. Because of this rapid biotransformation, parameters like $AUC_{0-\infty}$, $t_{1/2}$, V_{ss}, and CL could not be calculated since the terminal phase of the prodrug could not be characterized. Unchanged ceftaroline fosamil was not detected in urine, except for trace amounts in 0-2 hour samples for 4/6 subjects with severe renal impairment.

(ii) Ceftaroline (active metabolite): Both C_{max} and $AUC_{0-\infty}$ for ceftaroline were also significantly greater in subjects with severe renal impairment than in those with normal renal function, with geometric mean ratios 1.21 and 2.15, respectively. T_{max} generally occurred around the end of 1-hour IV infusion and did not differ between renal cohorts. Ceftaroline CL and CL_r decreased with decreasing renal function (as CrCL) in a relatively linear fashion (**Figure 3** and **Figure 4**), and Ae_{0-t} in urine was similarly lower in impaired subjects (22.88% versus 62.32%), while V_{ss} appeared unchanged. Accordingly, mean $t_{1/2}$ was extended in severe renal impairment (5.05 hours) versus normal renal function (3.02 hours), with corresponding slower elimination profiles.

(iii) Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline): Exposures C_{max} and $AUC_{0-\infty}$ for M-1 were significantly impacted by renal impairment (more so than ceftaroline or ceftaroline fosamil), with geometric mean ratios of 2.20 and 3.85, respectively. Consequently, $AUC_{0-\infty}$ ratios to the active ceftaroline (calculated by the Reviewer) were greater for the severe renal cohort (0.28-0.65) than the normal renal cohort (0.16-0.23). Similarly to ceftaroline, CL and CL_r for M-1 decreased with decreasing renal function (as CrCL) in a relatively linear fashion (**Figure 5** and **Figure 6**), with lower Ae_{0-t} recovered in urine for impaired subjects (3.83% versus 6.29%). Accordingly, mean $t_{1/2}$ was extended in severe renal impairment (7.05 hours) versus normal renal function (4.40 hours), with corresponding slower elimination profiles. However, unlike ceftaroline, mean V_{ss} for M-1 appeared to be lower in subjects with severe impairment (130.5 L) than in those with normal function (265.4 L).

As observed with mild and moderate renal impairment (from Study P903-02), T_{max} of M-1 was delayed in subjects with severe renal impairment, occurring between 5-9 hours post-dose versus approximately 1 hour for those with normal renal function (**Figure 7**).

Reviewer Comment: Occurrence of this higher and delayed peak in M-1 for renally impaired subjects is theorized as attributable to a combination of: 1) greater circulating concentrations of the active ceftaroline in impaired subjects, which translates to more ceftaroline available for conversion/degradation into the open-ring metabolite, M-1, and 2) longer elimination $t_{1/2}$ of M-1 versus ceftaroline that contributes to additional and delayed accumulation of M-1.

Table 3. Mean ± SD pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 following single 1-hour IV infusion of ceftaroline fosamil 400 mg in subjects with normal renal function and severe renal impairment

Parameter	Renal Function		Geometric Mean Ratio (90% CI)	p-value
	Normal 400 mg (n=6)	Severe 400 mg (n=6)		
Ceftaroline fosamil				
C_{max} (µg/mL)	1.29 ± 0.48	2.13 ± 1.00	1.65 (1.32-2.06)	0.0063
T_{max} (h)[a]	0.67 (0.33-1.35)	0.50 (0.33-0.67)	–	–
AUC_{0-t} (µg*h/mL)	0.94 ± 0.43	1.86 ± 0.96	2.04 (1.45-2.86)	0.0081
$AUC_{0-\infty}$ (µg*h/mL)	–[b]	–[b]	–	–
$t_{1/2}$ (h)	–[b]	–[b]	–	–
V_{ss} (L)	–[b]	–[b]	–	–
CL (L/h)	–[b]	–[b]	–	–
CL_r (L/h)	0.00	0.25 ± 0.27	–	–
Ae_{0-t} (% of dose)	0.00	0.10 ± 0.09	–	–
Ceftaroline				
C_{max} (µg/mL)	14.75 ± 1.82	17.87 ± 2.86	1.21 (1.10-1.32)	0.0091
T_{max} (h)[a]	1.08 (0.33-1.25)	1.25 (0.92-1.58)	–	–
AUC_{0-t} (µg*h/mL)	52.26 ± 10.54	112.4 ± 20.33	2.16 (1.99-2.34)	<0.0001
$AUC_{0-\infty}$ (µg*h/mL)	52.81 ± 10.51	113.3 ± 20.48	2.15 (1.99-2.33)	<0.0001
$t_{1/2}$ (h)	3.02 ± 0.43	5.05 ± 1.22	–	–
V_{ss} (L)	22.91 ± 3.97	20.74 ± 3.17	–	–
CL (L/h)	6.90 ± 1.44	3.22 ± 0.67	–	–
CL_r (L/h)	4.38 ± 1.13	0.71 ± 0.26	–	–
Ae_{0-t} (% of dose)	62.32 ± 4.02	22.88 ± 9.03	–	–
Ceftaroline M-1				
C_{max} (µg/mL)	0.97 ± 0.18	2.12 ± 0.35	2.20 (1.96-2.46)	<0.0001
T_{max} (h)[a]	1.08 (0.33-5.00)	7.05 (5.00-9.08)	–	–
AUC_{0-t} (µg*h/mL)	9.86 ± 2.37	39.64 ± 7.87	4.06 (3.08-5.34)	0.0002
$AUC_{0-\infty}$ (µg*h/mL)	10.54 ± 2.38	40.34 ± 7.73	3.85 (3.00-4.95)	0.0001
$t_{1/2}$ (h)	4.40 ± 0.55	7.05 ± 1.14	–	–
V_{ss} (L)	265.4 ± 38.05	130.5 ± 23.36	–	–
CL (L/h)	35.88 ± 8.10	9.31 ± 1.86	–	–
CL_r (L/h)	2.47 ± 1.04	0.37 ± 0.17	–	–
Ae_{0-t} (% of dose)	6.29 ± 1.53	3.83 ± 1.47	–	–

[a] Reported as median (minimum-maximum)
[b] Not able to be calculated

Figure 1. Mean ±SD **ceftaroline** concentrations following single doses of ceftaroline fosamil 400 mg as a 1-hour IV infusion in subjects with normal renal function and severe renal impairment

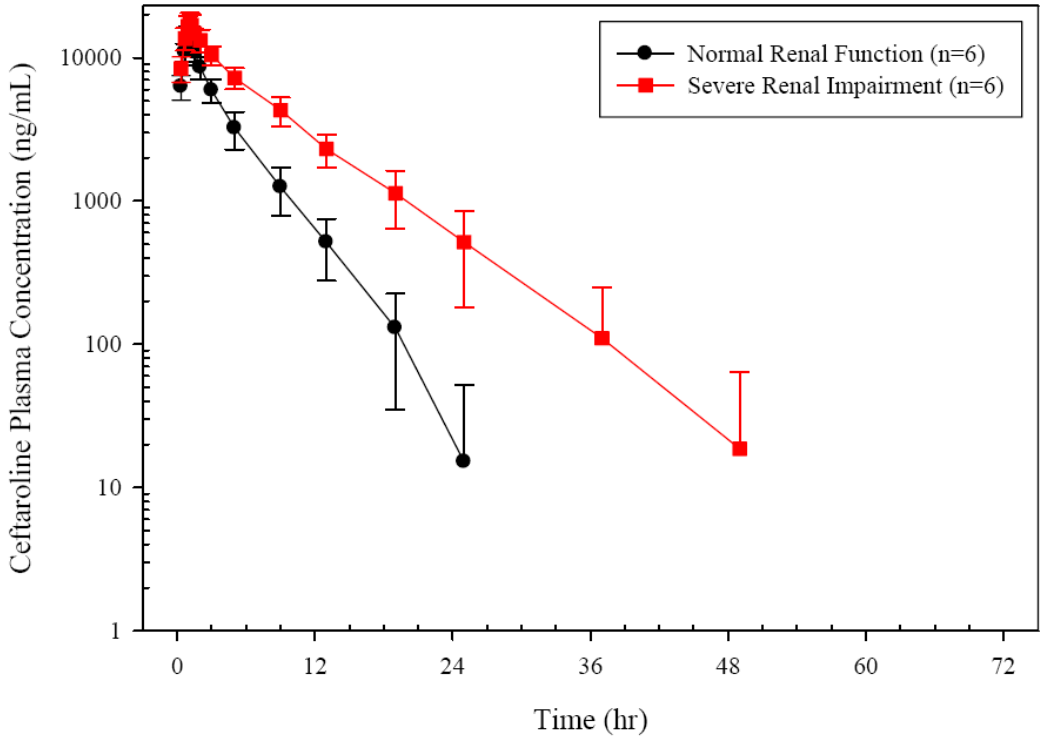


Figure 2. Mean ±SD **ceftaroline M-1** concentrations following single doses of ceftaroline fosamil 400 mg as a 1-hour IV infusion in subjects with normal renal function and severe renal impairment

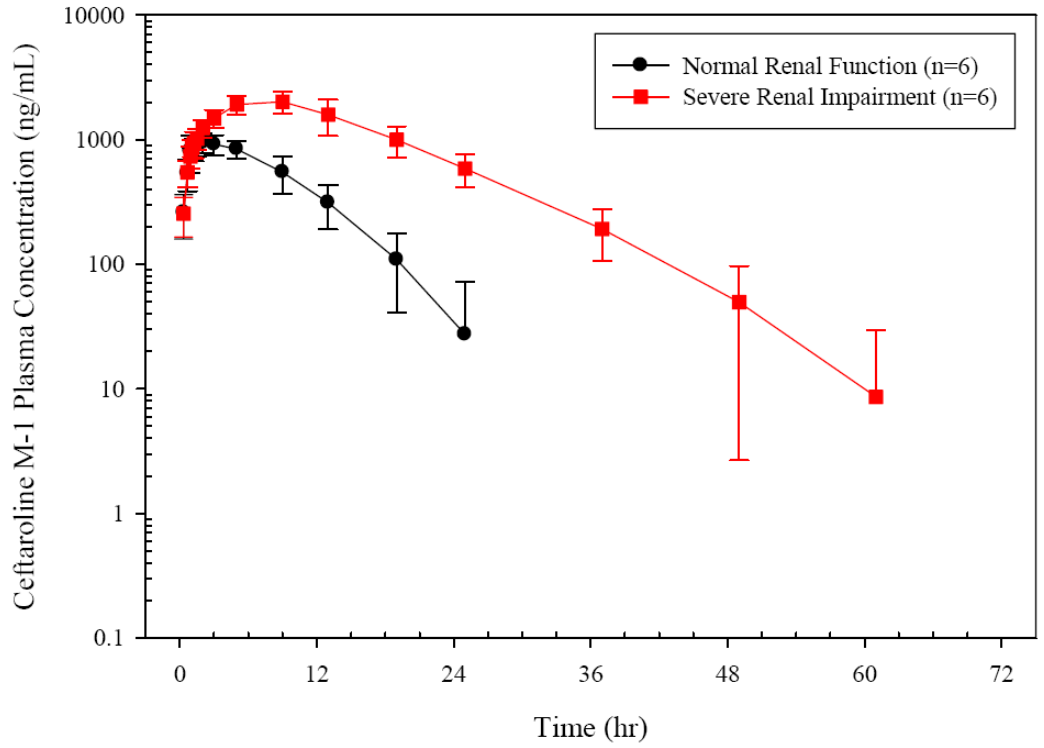


Figure 3. Relationship between **CrCL and ceftaroline CL** in subjects with normal renal function and severe renal impairment

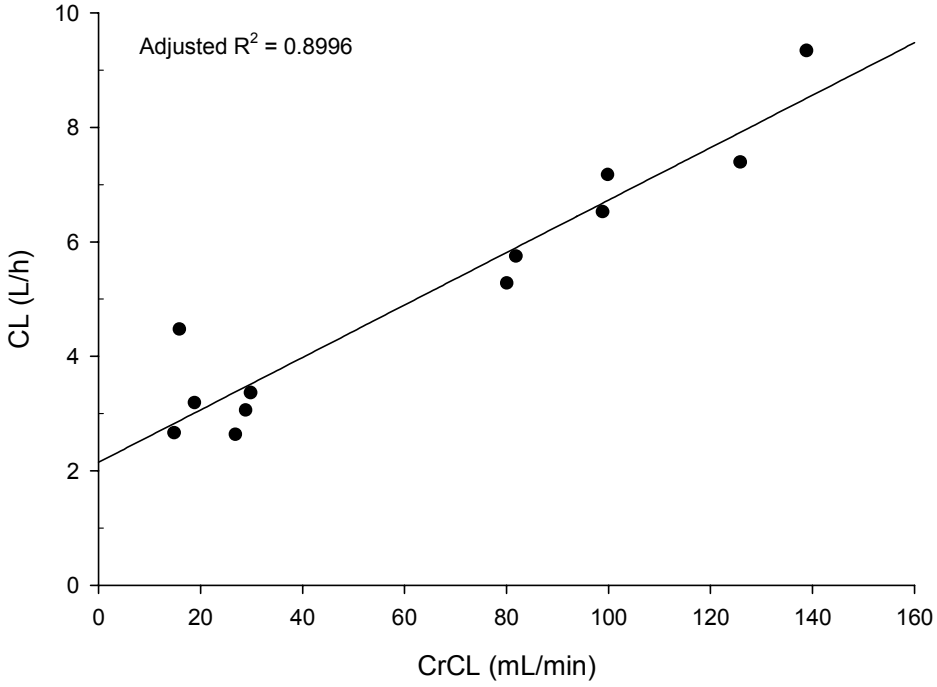


Figure 4. Relationship between **CrCL and ceftaroline CL_r** in subjects with normal renal function and severe renal impairment

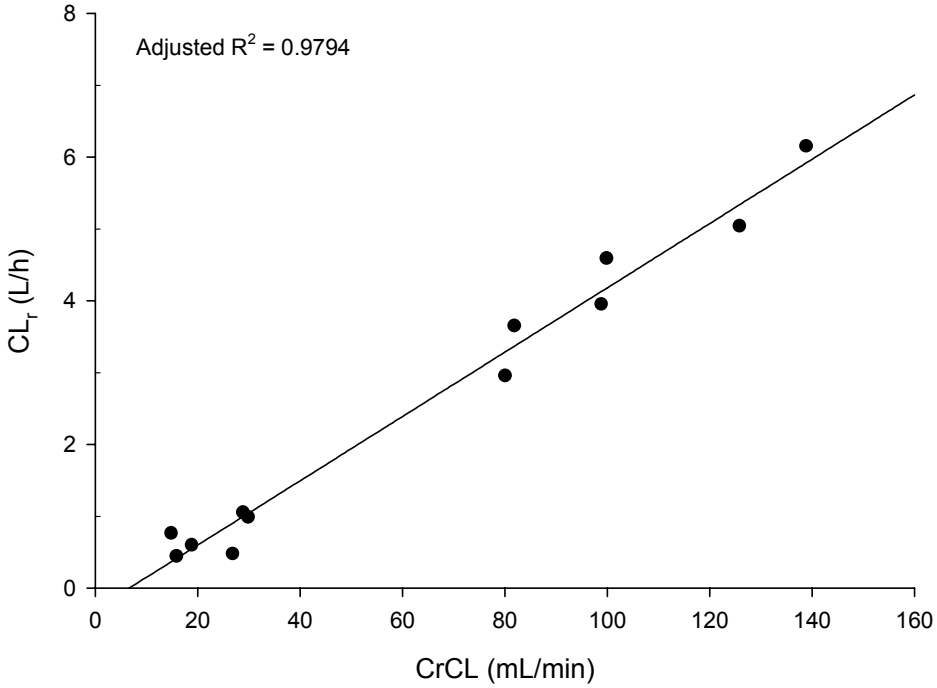


Figure 5. Relationship between **CrCL and ceftaroline M-1 CL** in subjects with normal renal function and severe renal impairment

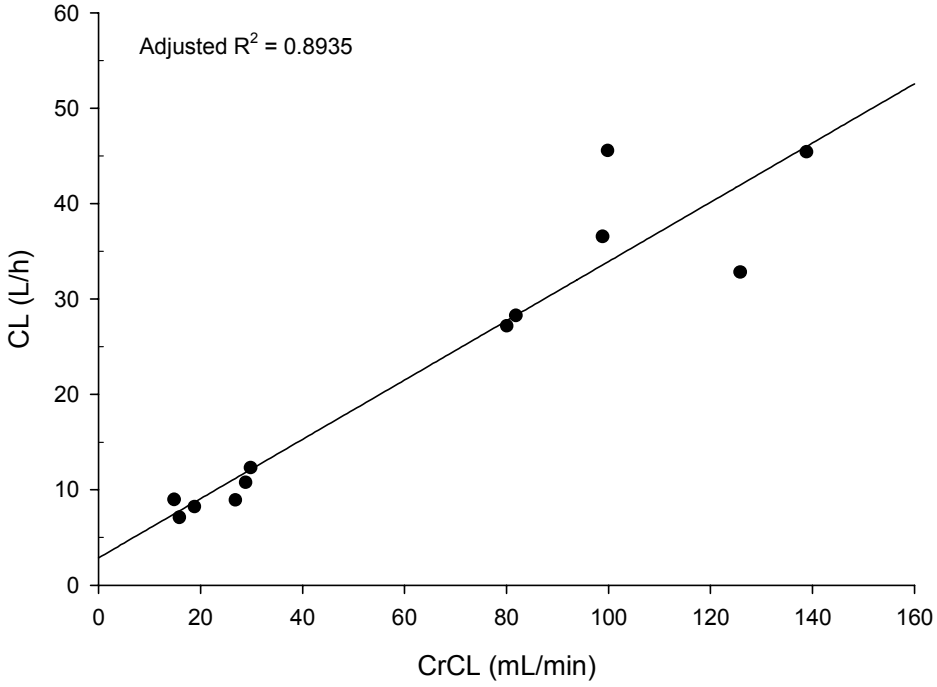


Figure 6. Relationship between **CrCL and ceftaroline M-1 CL_r** in subjects with normal renal function and severe renal impairment

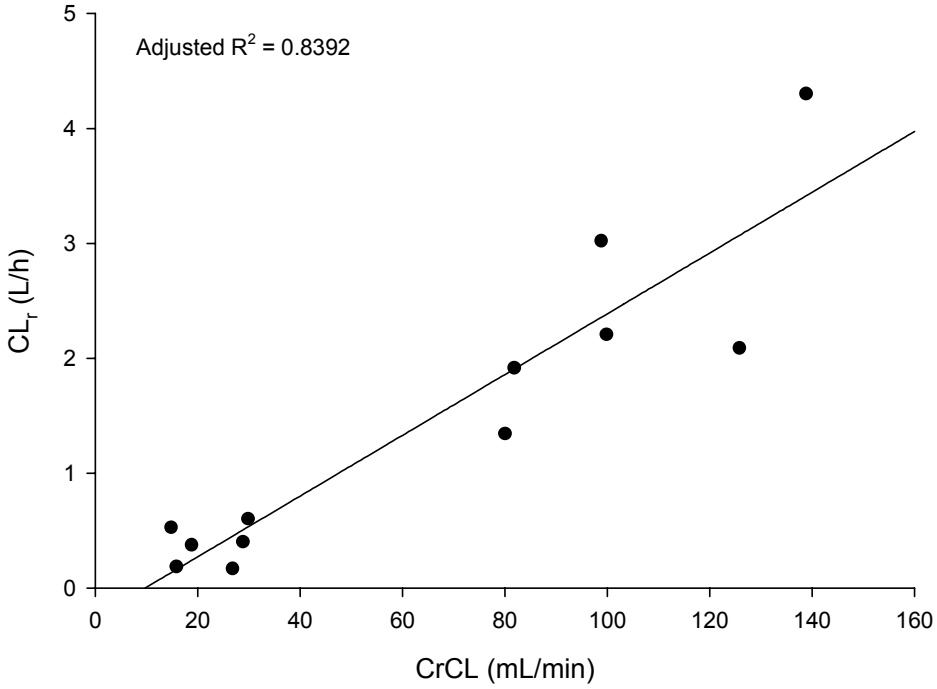
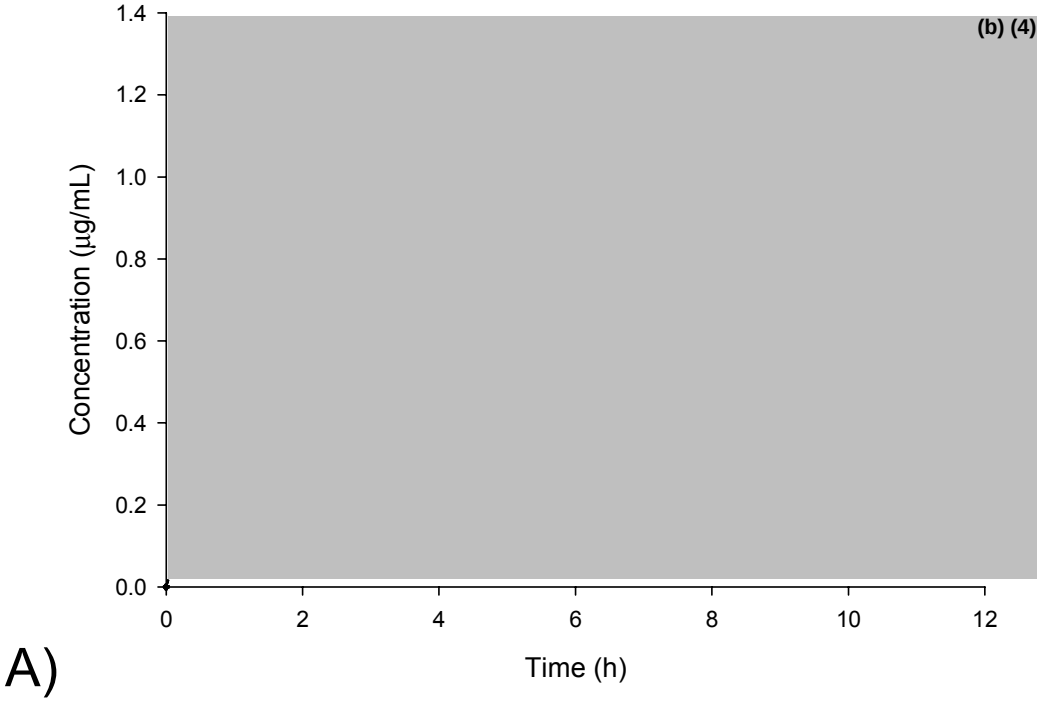
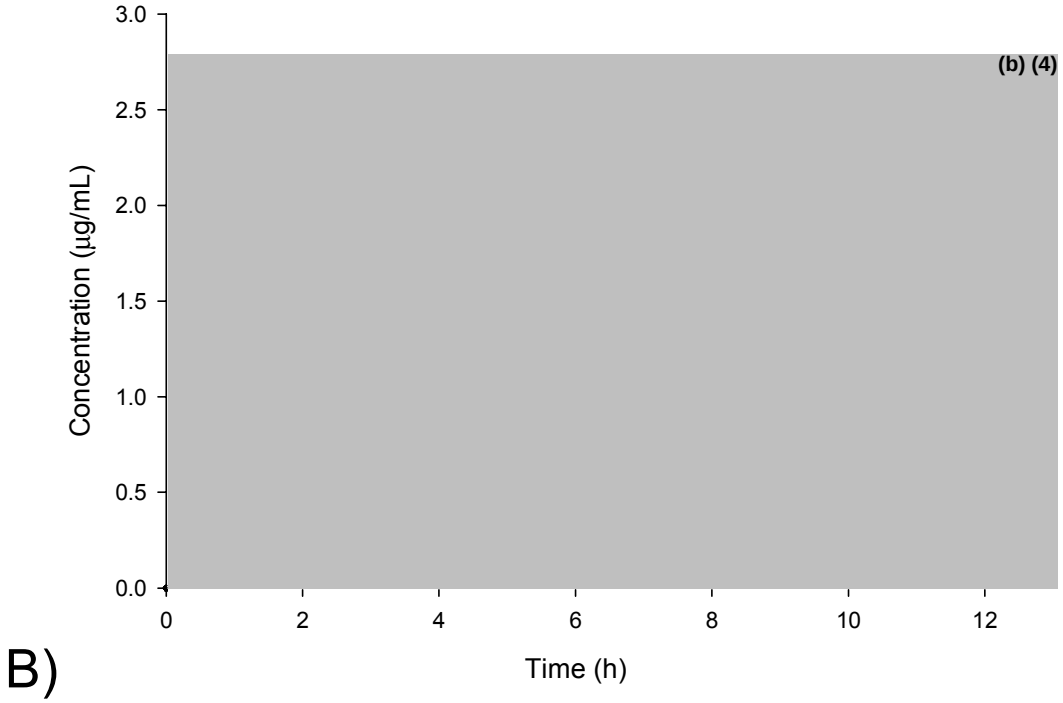


Figure 7. Individual **ceftaroline M-1** concentrations in subjects with **A)** normal renal function, and **B)** severe renal impairment



A)



B)

Safety: In total, 11 adverse events were reported by 7/12 (58%) subjects, and consisted of 7 events in 3/6 (50%) subjects with normal renal function cohort and 4 events in 4/6 (67%) subjects with severe renal impairment. The only event occurring in more than one subject was peripheral edema, which was reported in 2/12 (17%) subjects, one in each renal cohort; considered possibly related to study drug in the subject with severe renal impairment. With the exception of moderate myalgia and moderate back pain reported by one subject in the normal cohort, all events were considered mild in severity.

No clinically significant change in laboratory (chemistry, hematology, and urinalysis), vital signs, and electrocardiogram findings was noted.

SPONSOR'S CONCLUSIONS: Following single 1-hour IV infusion of ceftaroline fosamil 400 mg in subjects with normal renal function (CrCL >80 mL/min) and severe renal impairment (CrCL ≤30 mL/min):

- Pharmacokinetics of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 were all significantly altered in severe renal impairment; AUC values for those with severe renal impairment were 2-4 times that of subjects with normal renal function (geometric mean ratios 2.04, 2.15, and 3.85, respectively).
- Systemic exposure to ceftaroline was significantly greater in subjects with severe renal impairment than in subjects with normal renal function due to higher $t_{1/2}$, lower CL_r, and lower CL.
- There was a significant relationship between ceftaroline CL and CL_r with CrCL.
- Ceftaroline fosamil was well-tolerated in subjects with normal renal function and severe renal impairment; most adverse events were mild in severity and considered unrelated to study drug.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results. Data from Study P903-04 was used in the development of final population pharmacokinetic models, which were then used to predict the probability of (pharmacokinetic/pharmacodynamic) target attainment to assess appropriateness of renal adjusted dosing (Reports ICPD 00174-8 and ICPD 00174-9). (b) (4)

The Reviewer performed additional pharmacokinetic analyses to verify the appropriateness of ceftaroline fosamil 400 mg Q12 for subjects with severe renal impairment versus 600 mg Q12 for subjects with normal renal function using data from Study P903-04. Plasma concentration-time data of active ceftaroline following single 1-hour IV infusions of ceftaroline fosamil 400 mg were fitted for each individual subject using WinNonlin software (version 5.2.1, Pharsight Corporation, Mountain View, CA). A two-compartment IV infusion model with microconstants, no lag time, first-order elimination, and 1/y*y weighting was used. The model was selected based on visual inspection of fit and goodness of fit measured by the Akaike Information Criterion (AIC) and weighted R^2.

The ceftaroline-equivalent of the prodrug dose that was administered (0.883 × ceftaroline fosamil dose, or 353.2 mg) and actual infusion times were used. Time points with zero concentration values after dose administration were omitted. One subject from the normal renal

group (Subject 0092-04004) failed to receive the entire dose of study drug (244 of 250 mL administered) due to air block in the infusion line, and was therefore excluded from the Reviewer's pharmacokinetic analysis.

Once fitted, individual pharmacokinetic parameters were used to simulate ceftaroline fosamil regimens in subjects with normal renal function (n=5) and severe renal impairment (n=6) (**Table 4**). To check the accuracy of the 2-compartmental model, the Reviewer first simulated single 1-hour IV infusions of ceftaroline fosamil 400 mg (as done in Study P903-04), and compared simulated pharmacokinetic parameters of ceftaroline against those reported using the Sponsor's non-compartmental analysis (**Table 5**). Simulated results by the Reviewer were found to be similar to reported results by the Sponsor.

Table 4. Median (min-max) estimates of ceftaroline pharmacokinetic parameters used as input parameters for Reviewer simulations

Input Parameter	Normal Renal Function (n=5)[a]	Severe Renal Impairment (n=6)
V_1 (L)	15.30 (14.76-19.25)	12.25 (7.61-17.56)
K_{10} (1/h)	0.40 (0.37-0.69)	0.26 (0.16-0.42)
K_{12} (1/h)	0.44 (0.19-0.92)	0.80 (0.22-1.94)
K_{21} (1/h)	0.68 (0.53-1.27)	1.14 (0.41-1.60)

***k_{10}**, elimination rate constant; **k_{12}** and **k_{21}**, microtransfer rate constants between central and 2nd compartments; **V_1**, apparent volume of distribution of central compartment*
[a] *Excludes Subject 0092-04004 who received 244 of 250 mL of study drug*

Table 5. Ceftaroline pharmacokinetic parameters by Sponsor's non-compartmental analysis versus Reviewer's 2-compartmental analysis for subjects with normal renal function and severe renal impairment following single 1-hour IV infusions of ceftaroline fosamil 400 mg

Normal Renal Function						
Subject No.	0090-04002	0091-04006	0091-04007	0091-04008	0092-04001	0092-04004
C_{max} (µg/mL)						
Sponsor	15.36	13.61	16.56	12.42	16.95	13.61
Reviewer	16.98	14.54	16.78	11.66	15.33	–[a]
$AUC_{0-\infty}$ (µg*h/mL)						
Sponsor	67.10	37.86	61.56	47.86	54.26	48.22
Reviewer	61.92	34.42	57.22	45.72	50.07	–[a]
$t_{1/2}$ (h)						
Sponsor	3.74	2.45	2.98	3.25	2.82	2.91
Reviewer	3.65	2.35	2.94	3.23	2.87	–[a]
Severe Renal Impairment						
Subject No.	0090-04001	0090-04003	0091-04001	0091-04002	0091-04003	0092-04002
C_{max} (µg/mL)						
Sponsor	20.53	17.67	16.61	21.87	14.15	16.37
Reviewer	21.83	19.73	17.52	23.77	15.17	17.14
$AUC_{0-\infty}$ (µg*h/mL)						
Sponsor	133.26	105.43	111.22	115.99	79.20	134.80
Reviewer	128.56	100.18	105.06	110.83	75.82	129.28
$t_{1/2}$ (h)						
Sponsor	5.19	5.16	4.78	4.06	3.83	7.26
Reviewer	5.17	5.16	4.89	4.07	3.80	7.39

[a] *Subject 0092-04004 received 244 of 250 mL of study drug; excluded from Reviewer's analysis*

Accuracy of the 2-compartmental model confirmed, the Reviewer then simulated steady-state exposures of active ceftaroline for the standard regimen (ceftaroline fosamil 600 mg Q12 × 3 days) in subjects with normal renal function and various renal-adjusted regimens (ceftaroline fosamil 400 mg Q12 or 300 mg Q12 × 3 days) in those with severe renal impairment. For Reviewer simulations, the ceftaroline-equivalent of the prodrug dose (0.883 × ceftaroline fosamil dose) was used and all doses were 1-hour IV infusions. Calculation of %*f*T>MIC (target pharmacokinetic/pharmacodynamic parameter) assumed equal protein binding between renal groups (20%) and was determined in 0.2-hour increments over the dosing interval.

Geometric mean of simulated C_{max} in the severe group was 5% and 29% lower, respectively, with 400 mg Q12 (22.03 µg/mL; 106.61 µg*h/mL) and 300 mg Q12 (16.52 µg/mL; 79.96 µg*h/mL) regimens than the normal group (23.26 µg/mL; 73.33 µg*h/mL) (**Figure 8**), while AUC_{12} was 45% and 9% greater, respectively (**Figure 9**). Of simulated regimens, 300 mg Q12 was more suitable for subjects with severe renal impairment (b) (4) in matching ceftaroline AUC_{12} of the normal renal cohort. Moreover, individual %*f*T>MIC curves over theoretical bacterial MICs for the 300 mg Q12 regimen in those with severe renal impairment were comparable to or greater than that of the standard 600 mg Q12 regimen in subjects with normal renal function (**Figure 10**). Reviewer-simulated profiles of active ceftaroline following 600 mg Q12 × 3 days in subjects with normal renal function and 300 mg Q12 × 3 days in those with severe renal impairment are shown in **Figure 11**.

Based on Study P903-04 data, the renal-adjusted regimen of ceftaroline fosamil 300 mg Q12 appears to be appropriate for subjects with severe renal impairment (CrCL ≤30 mL/min), (b) (4), in matching ceftaroline exposures (as AUC and %*f*T>MIC) of the standard 600 mg Q12 regimen in subjects with normal renal function (CrCL >80 mL/min).

Figure 8. Individual **ceftaroline C_{max} at steady-state** in subjects with normal renal function and severe renal impairment, **simulated by the Reviewer**

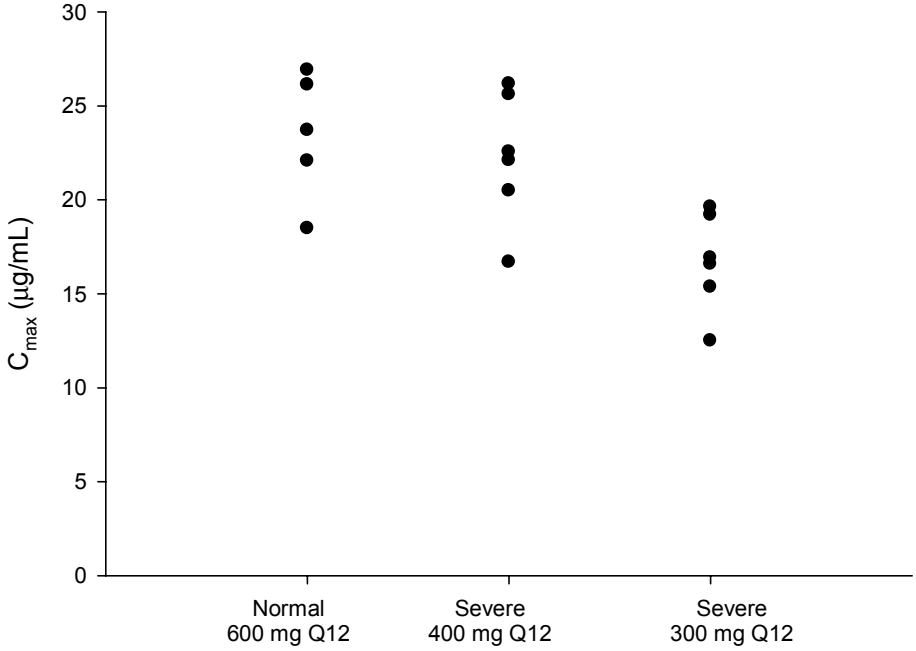


Figure 9. Individual **ceftaroline AUC_{12} at steady-state** in subjects with normal renal function and severe renal impairment, **simulated by the Reviewer**

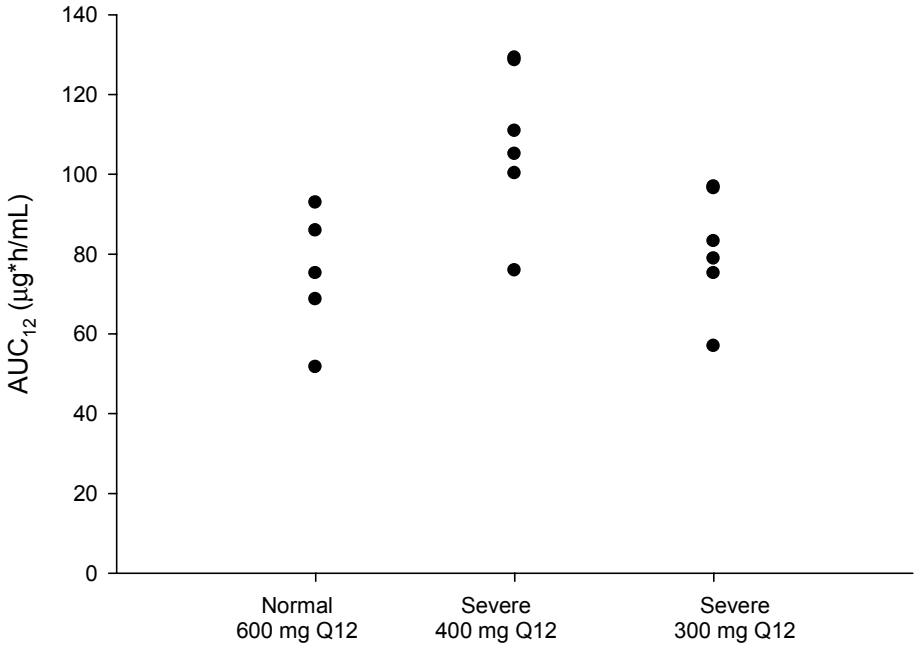


Figure 10. Individual **ceftaroline % *f*T>MIC at steady-state** in subjects with normal renal function and severe renal impairment, **simulated by the Reviewer**

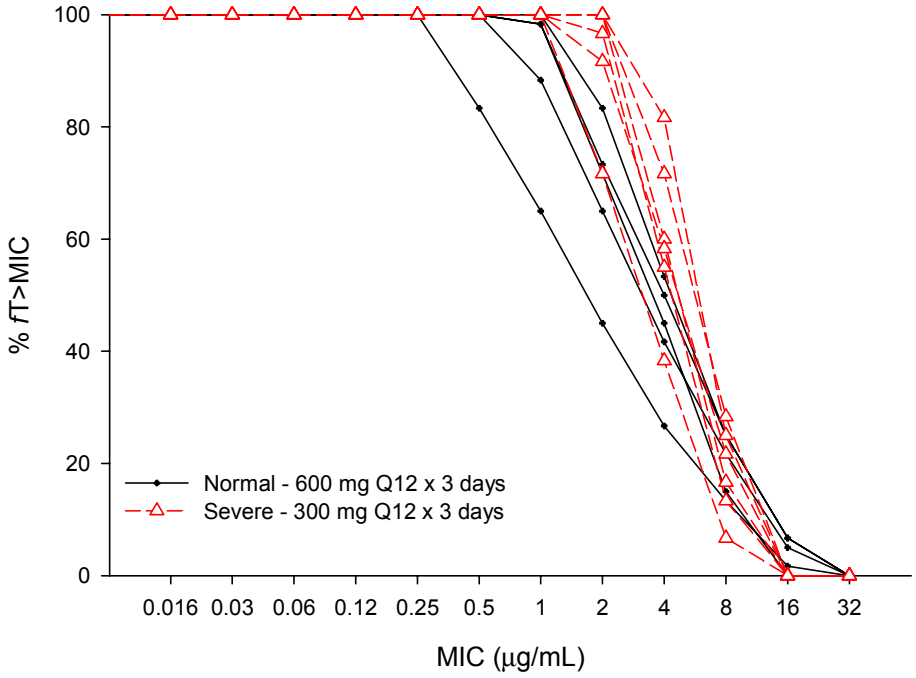
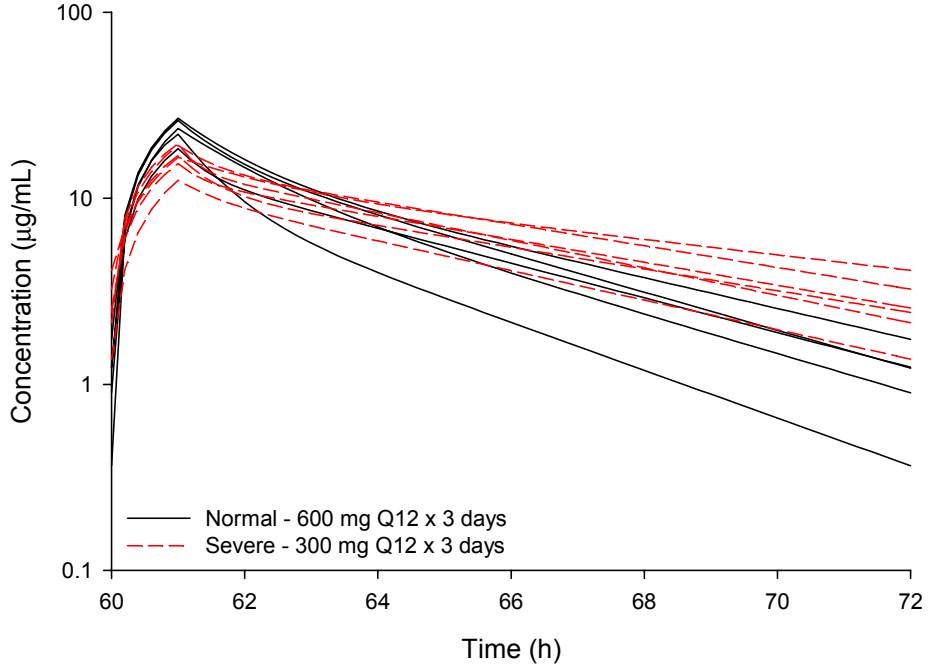


Figure 11. Individual **ceftaroline concentrations at steady-state** in subjects with normal renal function and severe renal impairment, **simulated by the Reviewer**



STUDY NO.: P903-11

An open-label pharmacokinetic, safety, and tolerability study of single intravenous doses of ceftaroline in healthy elderly and healthy young adult subjects

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Date(s): 18 Feb 2008 – 25 Jun 2008
Investigator(s): G Weiner, DO,
Clinical Site(s): Allied Research International Inc., Miami Gardens, FL
Analytical Site(s): (b) (4)

OBJECTIVE:

- To compare the pharmacokinetic profiles of ceftaroline in healthy elderly subjects (≥65 years of age) with those in healthy young adult subjects (18-45 years of age) who received a single IV dose of ceftaroline fosamil
- To evaluate the safety and tolerability of a single IV dose of ceftaroline fosamil in healthy elderly subjects

METHODS

Study Design: P903-11 was a single-center, open-label, parallel-group, single-dose study conducted in healthy adults (n=32, total) as follows:

- Healthy elderly subjects (n=16): ≥65 years of age (at least 8 subjects ≥75 years of age)
- Healthy young adult subjects (n=16): 18-45 years of age

Inclusion Criteria: Males and females (using effective method of birth control), either ≥65 years of age or 18-45 years of age (inclusive), and 18-35 kg/m^2 (inclusive) in body mass index (BMI) were enrolled. Creatinine clearance (CrCL), as estimated with Cockcroft-Gault, was required to be ≥60 mL/min for elderly subjects and ≥80 mL/min for young adults.

Treatment: Ceftaroline fosamil was administered as a single 600 mg IV dose over 1 hour. Powder containing ceftaroline fosamil and L-arginine (excipient) was reconstituted with Sterile Water for Injection, and then transferred into an infusion bag/bottle of 250 mL of 0.9% sodium chloride solution. The prepared infusion bag/bottle was stored at 2-8 ºC for no longer than 24 hours and used within 6 hours after preparation or after removal from refrigerated storage.

Probenecid and diuretics were prohibited from time of enrollment and throughout the study. Concomitant medications, including over-the-counter analgesics, vitamin preparations, herbal preparations, nutritional supplements, and cough syrup, were prohibited from 14 days prior to dosing, while hormonal drug products were prohibited from 30 days prior. For elderly subjects, medically necessary medications for treatment of well-controlled common medical conditions were permitted on a case-by-case basis.

Subjects fasted overnight the night before the Study Day, and standardized meals, snacks, and beverages were provided during confinement. Subjects were to refrain from drinking fluids for 1

hour before and 1 hour after study drug administration. Subjects were required to abstain from alcohol within 72 hours before and caffeine or grapefruit-containing products within 48 hours before Study Day.

Sample Collection: Plasma and urine samples were collected (**Table 1**) and analyzed for pharmacokinetic purposes.

Table 1. Pharmacokinetic sampling scheme for single 1-hour IV infusion of ceftaroline fosamil 600 mg

Plasma	• Pre-dose • 20, 40, and 60 (immediately before end of infusion), 65, 75, and 90 min, and 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 h AFTER START of infusion
Urine	• Pre-dose • 0-2, 2-4, 4-8, 8-12, 12-24, and 24-48 h AFTER START of infusion

Analytical Methods: Pharmacokinetic samples were analyzed for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 by validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays for plasma (Method 3; PRD-RPT-BDM-00077, 2009) and for urine (Method 4; PRD-RPT-BDM-00080, 2008) (**Table 2**).

Table 2. Bioanalytical results of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma and urine

Criterion	Ceftaroline fosamil	Ceftaroline	Ceftaroline M-1	Comments
PLASMA				
Range	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	0.05-20 µg/mL (1:10 dilution tested with 16 µg/mL)	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	Satisfactory
LLOQ	0.05 µg/mL	0.05 µg/mL	0.05 µg/mL	Satisfactory
Linearity	R^2 ≥0.9963	R^2 ≥0.9956	R^2 ≥0.9905	Satisfactory
Accuracy	Within ±3.8%	Within ±5.7%	Within ±6.0%	Satisfactory
Precision	≤4.0 %CV	≤3.7 %CV	≤5.3 %CV	Satisfactory
Stability	• Study Dates: 18 Feb 2008 – 25 Jun 2008 • Analysis Dates: 18 Aug 2008 – 2 Sep 2008 • Stability: 526 days at -70 ºC			Satisfactory
URINE				
Range	0.5-5 µg/mL (1:5 dilution tested with 3.8 µg/mL)	0.5-50 µg/mL (1:9 dilution tested with 38 µg/mL)[a]	0.5-50 µg/mL (1:9 dilution tested with 38 µg/mL)[a]	**Unsatisfactory**[b]
LLOQ	0.5 µg/mL	0.5 µg/mL	0.5 µg/mL	Satisfactory
Linearity	R^2 ≥0.9953	R^2 ≥0.9961	R^2 ≥0.9966	Satisfactory
Accuracy	Within ±4.0%	Within ±5.1%	Within ±2.0%	Satisfactory
Precision	≤3.4 %CV	≤3.9 %CV	≤4.6 %CV	Satisfactory
Stability	• Study Dates: 18 Feb 2008 – 25 Jun 2008 • Analysis Dates: 10 Sep 2008 – 7 Nov 2008 • Stability: 469 days at -70 ºC			Satisfactory

[a] *Dilution integrity was evaluated further for ceftaroline and M-1 in urine during analysis for Study P903-11*
[b] *Ceftaroline concentrations in urine exceed the standard curve range even after 1:9 dilution in certain samples; results will be interpreted for qualitative and not quantitative purposes*

Pharmacokinetic Assessment: Pharmacokinetic parameters for ceftaroline fosamil, ceftaroline, ceftaroline M-1 were determined using non-compartmental methods. Since doses were expressed in terms of anhydrous, acetate-free ceftaroline fosamil (MW, 684.68), corrections were made to the dose when calculating parameters for ceftaroline (MW, 604.70; 0.883 ×

ceftaroline fosamil dose) and ceftaroline M-1 (MW, 622.72; 0.909 × ceftaroline fosamil dose). Parameters included the following:

- C_{max}, maximum observed plasma concentration
- AUC_{0-t}, area under the curve up to time corresponding to the last measurable concentration
- $AUC_{0-\infty}$, area under the curve from time 0 to infinity
- T_{max}, corresponding time of C_{max}
- $t_{1/2}$, elimination half-life
- CL, plasma clearance
- V_{ss}, steady-state volume of distribution
- Ae_{0-t}, cumulative amount of drug excreted during entire urine collection period from time 0 to time t
- CL_r, renal clearance

Statistical Methods: Pharmacokinetic parameters for healthy elderly subjects and healthy young adult subjects were compared using Statistical Analysis System (SAS) Version 9.1 by analysis of covariance (ANCOVA), with age group as a factor. In order to evaluate the contribution of reduced renal function in elderly subjects to increases in ceftaroline and M-1 systemic exposure, additional analyses were performed by ANCOVA, with age group, CrCL, and age group by CrCL interaction as factors. The interaction term of age group by CrCL was not significant for all analyses and was later dropped from the model.

RESULTS

Study Population: In total, 33 subjects were enrolled, 17 healthy elderly and 16 healthy young adult subjects. One elderly subject (0001-11109) did not receive the full dose, and was subsequently replaced with an additional subject. There were 17 females and 16 males; 7 elderly females, 10 elderly males, 10 young adult females, and 6 young adult males. Mean ± SD age was 72.2 ± 6.0 years in the elderly group and 30.6 ± 7.0 years in the young adult group. Weight ranged 49.1-107.1 kg across age groups, with 70.8 ± 10.0 and 71.4 ± 16.6 kg for elderly and young adults, respectively. BMI ranged 20.2-34.8 kg/m^2 across age groups, with 27.5 ± 2.7 and 25.8 ± 3.9 kg/m^2 for elderly and young adults, respectively. CrCL ranged 61.2-106.9 mL/min for elderly subjects and 106.1-159.4 mL/min for young adults; 9/17 elderly subjects had mild renal impairment defined as CrCL >50 and ≤80 mL/min.

There were 8 elderly subjects ≥75 years old; age ranging 75-81 years. CrCL for these subjects ranged 61.2-85.9 mL/min; 6/8 subjects had mild renal impairment defined as CrCL >50 and ≤80 mL/min.

Pharmacokinetics: Pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in healthy elderly and healthy young adult subjects are listed in **Table 3**. Concentration-time profiles of ceftaroline and ceftaroline M-1 are displayed in **Figures 1** and **2**, respectively. There were no pharmacokinetic parameters with coefficient of variation (%CV) >50% except for M-1 T_{max} for the healthy young adult group.

(i) Ceftaroline fosamil (prodrug): Both C_{max} and AUC_{0-t} were only slightly greater in elderly subjects than in young adults, with geometric mean ratios of 1.12 and 1.14, respectively. T_{max} expectedly occurred during the 1-hour IV infusion regardless of age group due to rapid

conversion to active ceftaroline. Because of this rapid biotransformation, parameters like $AUC_{0-\infty}$, $t_{1/2}$, V_{ss}, and CL could not be accurately calculated for all subjects since the terminal phase of the prodrug could not be characterized. Unchanged ceftaroline fosamil was not detected in urine in any subject.

When grouped by elderly males and females versus young adult males and females (by the Reviewer), there was trend for slightly higher mean C_{max} (19-25%) and AUC_{0-t} (12-31%) in females.

(ii) Ceftaroline (active metabolite): Ceftaroline C_{max} was unaffected by age with a geometric mean ratio of 1.02, while $AUC_{0-\infty}$ was greater in elderly subjects than young adults with a geometric mean ratio of 1.33. T_{max} generally occurred around the end of 1-hour IV infusion and did not differ between groups. Ceftaroline CL and CL_r were expectedly lower (by 25% and 32%, respectively) in elderly subjects due to lower CrCL in the older cohort (half with mild renal impairment), as was Ae_{0-t} in urine, while mean V_{ss} appeared to be greater instead (elderly, 17.86 L; young adult, 15.84 L). Accordingly, mean $t_{1/2}$ was extended by 41% in elderly subjects (3.1 hours) than in young adults (2.2 hours), with corresponding slower elimination profiles.

In the ANCOVA analysis with CrCL as a factor, p-values for ceftaroline C_{max} and $AUC_{0-\infty}$ were 0.0554 and 0.0047, respectively, whereas those with age as a factor were 0.1751 and 0.2606, respectively. CrCL was a significant factor in accounting for greater systemic exposures of ceftaroline in elderly subjects, while age, by itself, was not. Thus, modest increases in ceftaroline $AUC_{0-\infty}$ in healthy elderly subjects are largely due to decreased renal function versus healthy young adults.

When grouped by elderly males and females versus young adult males and females (by the Reviewer), there was a trend for slightly higher mean C_{max} (17%) and $AUC_{0-\infty}$ (6-15%) of ceftaroline in females (**Figures 3** and **4**). Mean estimates of ceftaroline CL and V_{ss} were 6-12% and 20-21% lower, respectively, in females versus males across age groups, and differences in exposures could be partly attributed to lower body weight in females based on relationships with CL and V_{ss} (**Figures 5** and **6**).

(iii) Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline): Exposures C_{max} and $AUC_{0-\infty}$ for M-1 were impacted by elderly age more so than ceftaroline or ceftaroline fosamil, with geometric mean ratios of 1.11 and 1.48, respectively. Consequently, $AUC_{0-\infty}$ ratios to active ceftaroline (calculated by the Reviewer) were greater in the elderly cohort (0.21 ± 0.03) than the young adult cohort (0.19 ± 0.03). As observed with renal impairment (from Studies P903-02, P903-04, and P903-18), T_{max} of M-1 was slightly delayed in elderly subjects, occurring at 3 hours post-dose versus ~1 hour for young adults. Similarly to ceftaroline, CL and CL_r for M-1 were lower (by 32% for both) in elderly subjects due to lower CrCL in the older cohort (half with mild renal impairment), while mean Ae_{0-t} in urine was similar between groups. (It should be noted that % of dose renally excreted as M-1 was variable in young adults.) Accordingly, mean $t_{1/2}$ was extended by 24% in elderly subjects (4.6 hours) than in young adults (3.7 hours), with corresponding slower elimination profiles. However, unlike ceftaroline, mean V_{ss} for M-1 appeared to be lower in elderly subjects (226.1 L) than in young adults (252.8 L).

In the ANCOVA analysis with CrCL as a factor, p-values for M-1 C_{max} and $AUC_{0-\infty}$ were 0.1479 and 0.0067, respectively, whereas those with age as a factor were 0.7602 and 0.2321, respectively. Similarly to ceftaroline, CrCL was a significant factor in accounting for greater systemic exposures of M-1 in elderly subjects, while age, by itself, was not. Thus, modest increases in M-1 $AUC_{0-\infty}$ in healthy elderly subjects are largely due to decreased renal function versus healthy young adults.

When grouped by elderly males and females versus young adult males and females (by the Reviewer), there was a trend for slightly higher mean C_{max} (20-24%) and $AUC_{0-\infty}$ (7-13%) of ceftaroline M-1 in females (**Figures 7** and **8**). Mean estimates of ceftaroline M-1 CL and V_{ss} were 7-12% and 19-24% lower, respectively, in females versus males across age groups, and differences in exposures could be partly attributed to lower body weight in females based on relationships with CL and V_{ss} (**Figures 9** and **10**).

Table 3. Mean ± SD pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 following single 1-hour IV infusions of ceftaroline fosamil 600 mg in healthy elderly and healthy young adult subjects

Parameter	Healthy Elderly 600 mg (n=16)	Healthy Young Adult 600 mg (n=16)	Geometric Mean Ratio[a] (90% Confidence Interval)	p-value
Ceftaroline fosamil				
C_{max} (µg/mL)	3.43 ± 0.81	3.07 ± 0.70	1.12 (0.97-1.29)	–
T_{max} (h)[b]	0.38 (0.33-1.02)	0.67 (0.33-0.92)	–	–
AUC_{0-t} (µg*h/mL)	2.58 ± 0.51	2.33 ± 0.53	1.12 (0.98-1.28)	–
$AUC_{0-\infty}$ (µg*h/mL)	3.03 ± 0.45[c]	2.66 ± 0.42[d]	1.14 (0.95-1.37)	–
$t_{1/2}$ (h)	0.06 ± 0.03[c]	0.06 ± 0.01[d]	–	–
V_{ss} (L)	21.98 ± 9.71[c]	20.96 ± 6.48[d]	–	–
CL (L/h)	201.3 ± 28.65[c]	230.9 ± 38.89[d]	–	–
CL_r (L/h)	–	–	–	–
Ae_{0-t} (% of dose)	–	–	–	–
Ceftaroline				
C_{max} (µg/mL)	31.82 ± 4.58	31.00 ± 3.79	1.02 (0.94-1.11)	0.6326
T_{max} (h)[b]	1.01 (0.93-1.1)	1.02 (0.88-1.1)	–	–
AUC_{0-t} (µg*h/mL)	94.05 ± 13.64	70.49 ± 10.09	1.33 (1.23-1.45)	<0.0001
$AUC_{0-\infty}$ (µg*h/mL)	94.06 ± 13.60	70.49 ± 10.09	1.33 (1.23-1.45)	<0.0001
$t_{1/2}$ (h)	3.1 ± 0.4	2.2 ± 0.4	–	–
V_{ss} (L)	17.86 ± 2.95	15.84 ± 2.73	–	–
CL (L/h)	5.74 ± 0.81	7.64 ± 0.90	–	–
CL_r (L/h)	3.29 ± 0.76	4.86 ± 1.40	–	–
Ae_{0-t} (% of dose)	57.4 ± 11.7	64.5 ± 9.9	–	–
Ceftaroline M-1				
C_{max} (µg/mL)	1.75 ± 0.33	1.57 ± 0.29	1.11 (1.00-1.24)	0.1057
T_{max} (h)[b]	3.00 (1.03-4.00)	1.08 (1.00-4.00)	–	–
AUC_{0-t} (µg*h/mL)	19.26 ± 3.64	12.92 ± 2.53	1.49 (1.33-1.67)	<0.0001
$AUC_{0-\infty}$ (µg*h/mL)	19.35 ± 3.65	13.07 ± 2.46	1.48 (1.32-1.66)	<0.0001
$t_{1/2}$ (h)	4.6 ± 0.6	3.7 ± 0.5	–	–
V_{ss} (L)	226.1 ± 48.94	252.8 ± 46.48	–	–
CL (L/h)	29.11 ± 5.34	43.09 ± 7.96	–	–
CL_r (L/h)	1.69 ± 0.52	2.47 ± 0.76	–	–
Ae_{0-t} (% of dose)	5.7 ± 1.1	5.8 ± 2.0	–	–

[a] *Reference population = Young Adults*
[b] *Reported as median (minimum-maximum)*
[c] *Data from n=4*
[d] *Data from n=7*

Figure 1. Mean ±SD **ceftaroline** concentrations following single doses of ceftaroline fosamil 600 mg as a 1-hour IV infusion in healthy elderly and healthy young adult subjects

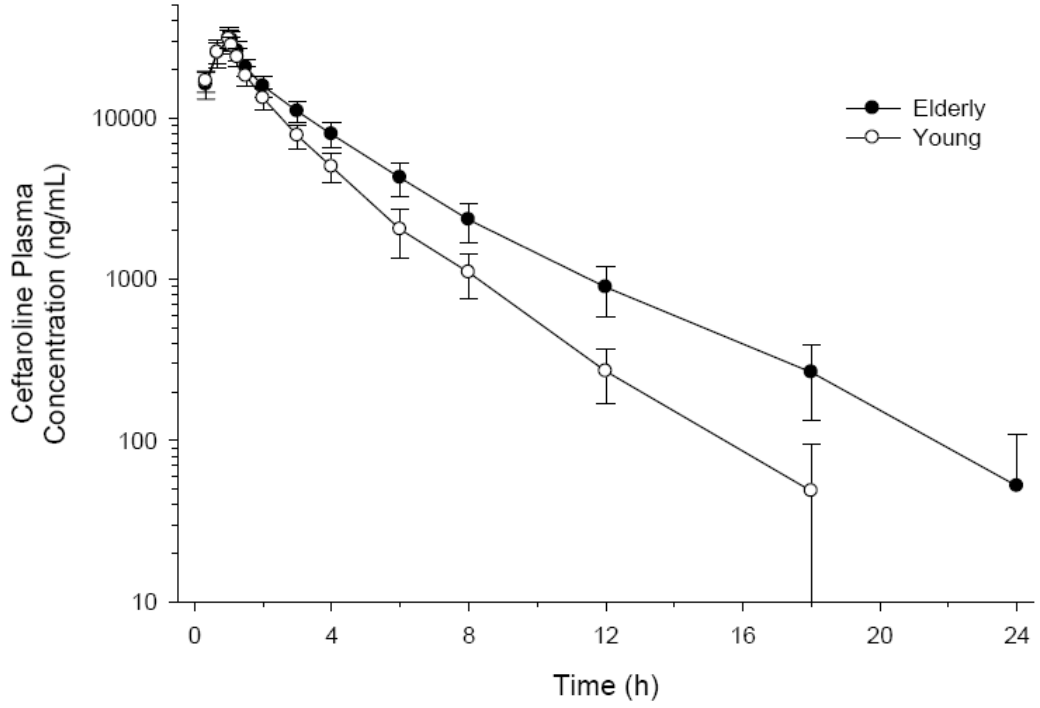


Figure 2. Mean ±SD **ceftaroline M-1** concentrations following single doses of ceftaroline fosamil 600 mg as a 1-hour IV infusion in healthy elderly and healthy young adult subjects

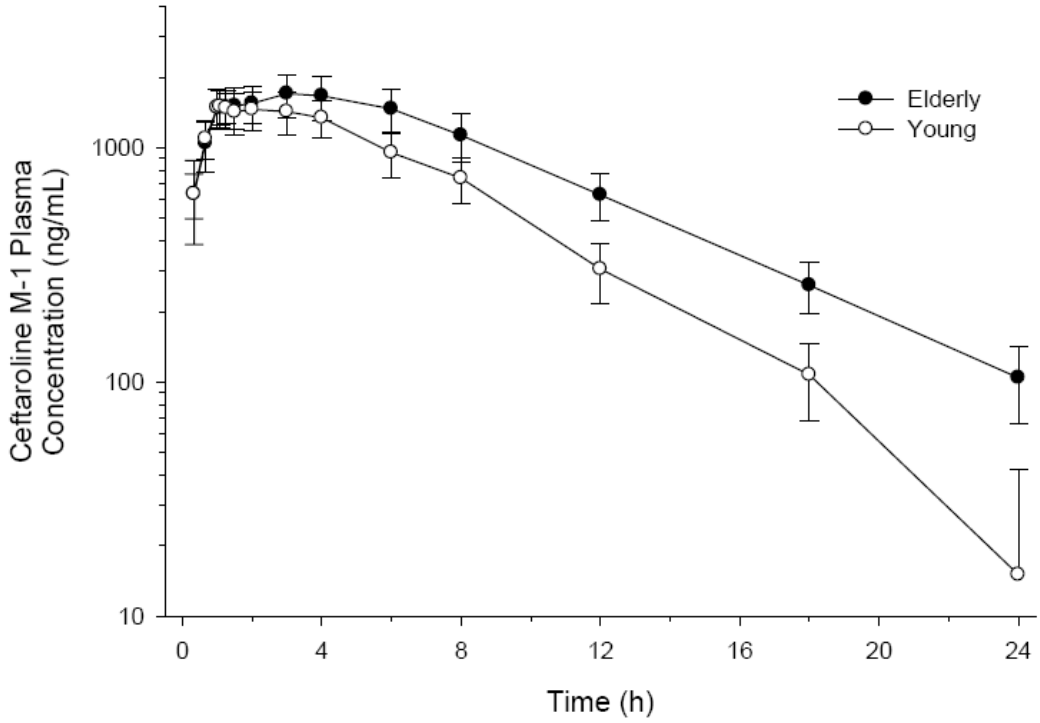


Figure 3. Individual **ceftaroline C_{max}** in healthy elderly and young adult males and females

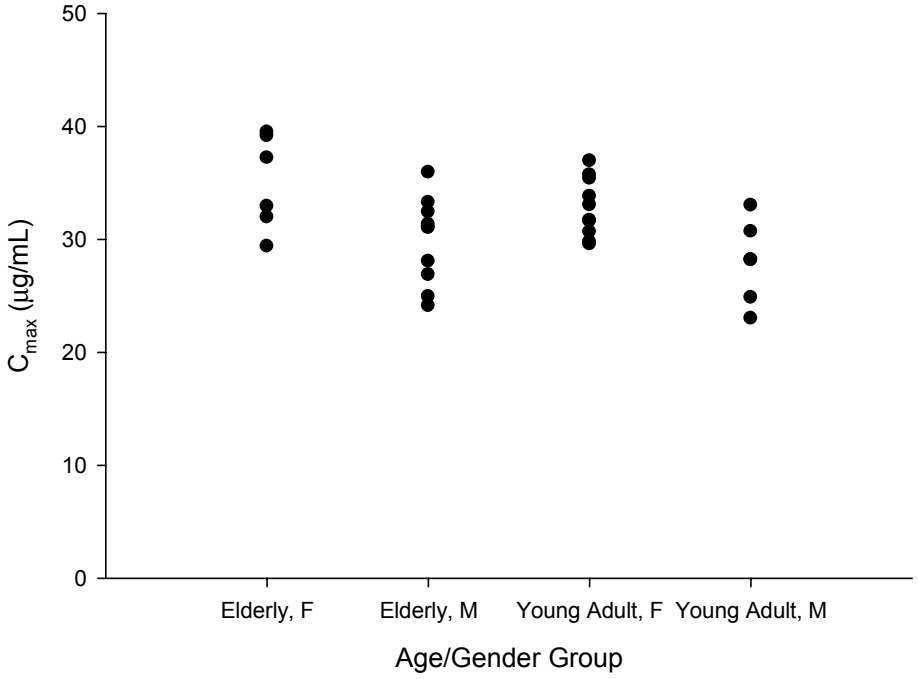


Figure 4. Individual **ceftaroline $AUC_{0-\infty}$** in healthy elderly and young adult males and females

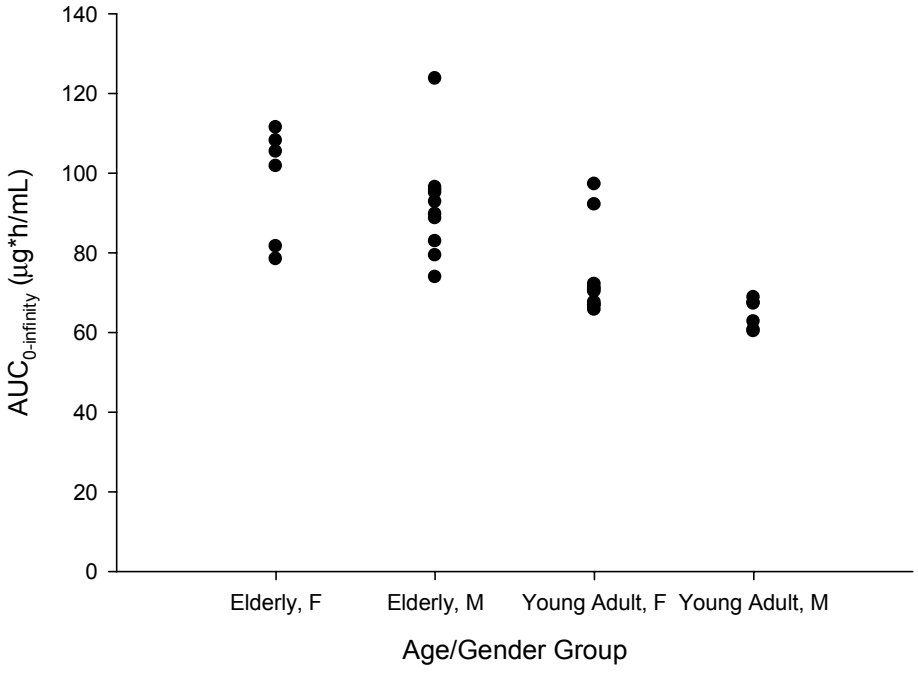


Figure 5. Relationship between body weight and **ceftaroline CL** in healthy elderly and young adult males and females

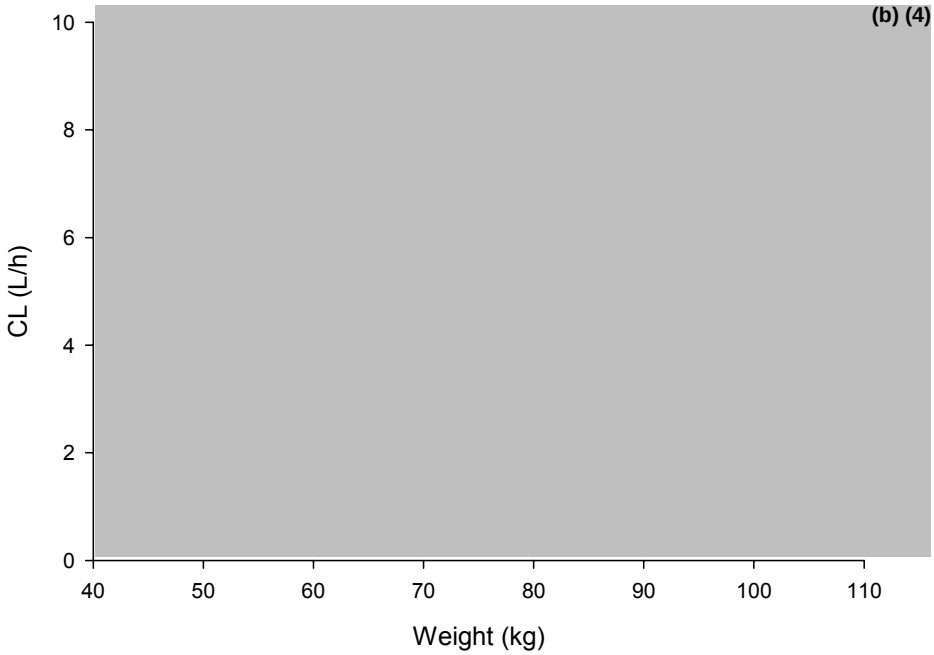


Figure 6. Relationship between body weight and **ceftaroline V_{ss}** in healthy elderly and young adult males and females

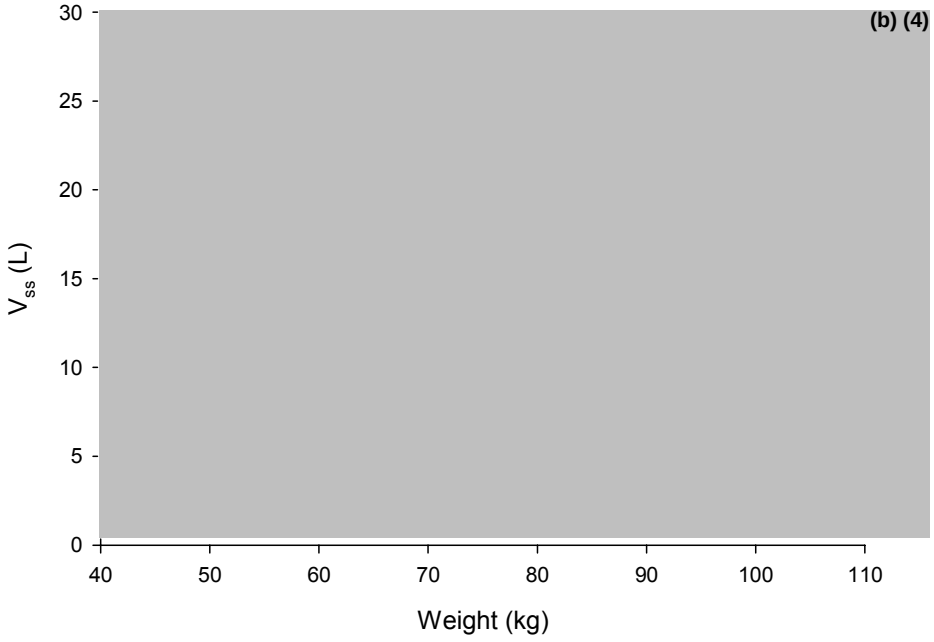


Figure 7. Individual **ceftaroline M-1 C_{max}** in healthy elderly and young adult males and females

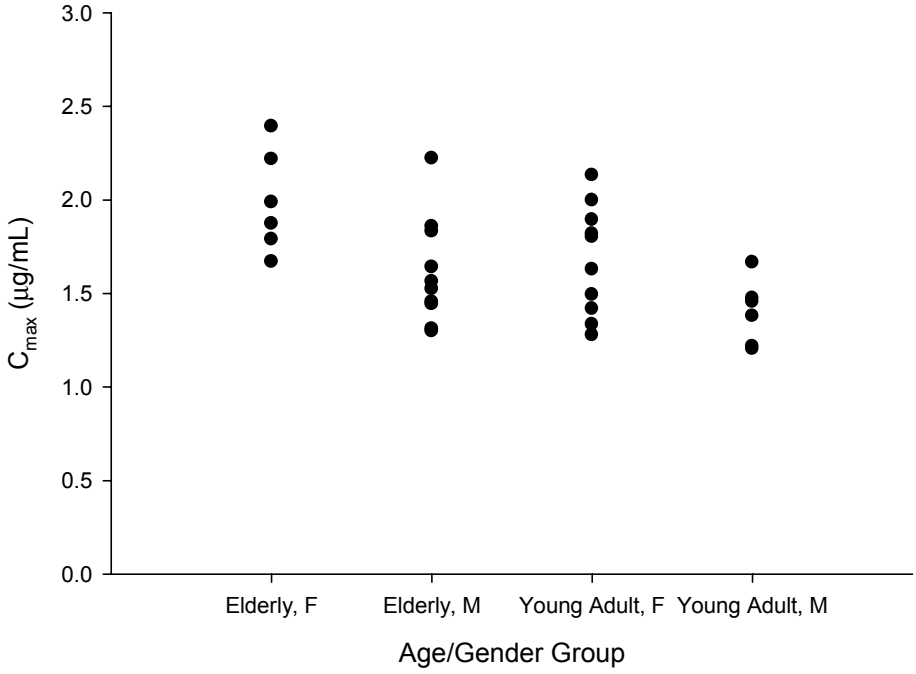


Figure 8. Individual **ceftaroline M-1 $AUC_{0-\infty}$** in healthy elderly and young adult males and females

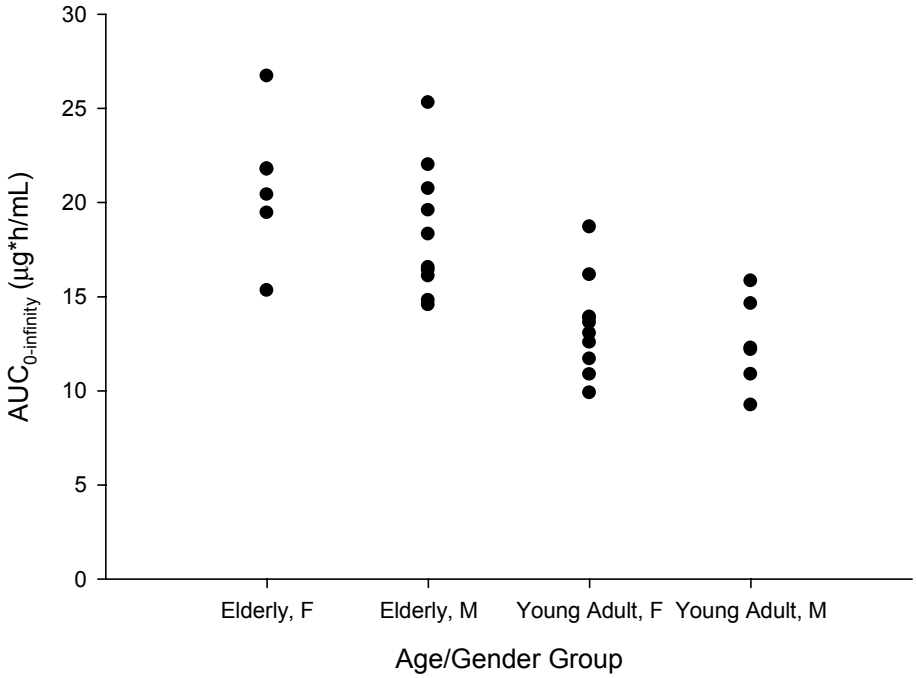


Figure 9. Relationship between body weight and **ceftaroline M-1 CL** in healthy elderly and young adult males and females

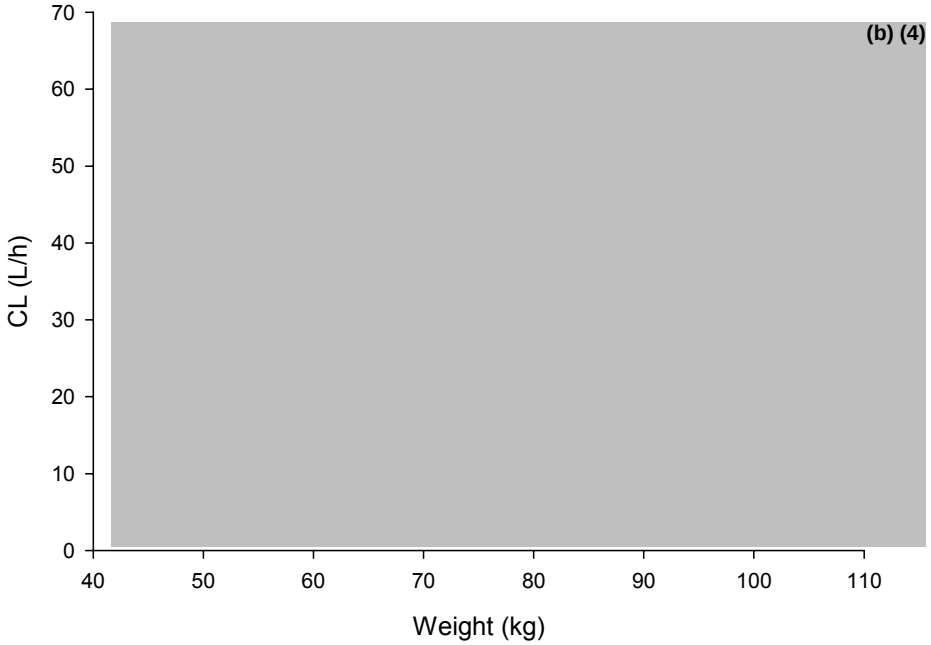
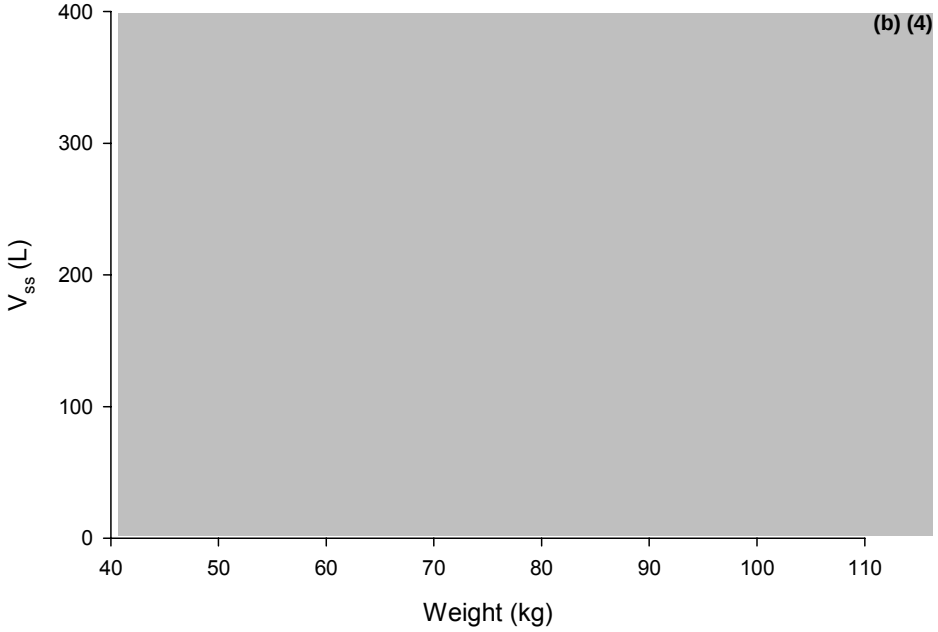


Figure 10. Relationship between body weight and **ceftaroline M-1 V_{ss}** in healthy elderly and young adult males and females



Safety: In total, 6 adverse events were reported by 5/33 (15%) subjects, and consisted of 5 events in 4/17 (24%) elderly subjects and 1 event in 1/16 (6%) young adults. The most commonly reported event was mild headache (n=3; 1 unrelated to study drug) in 1 elderly subject and 1 young adult. Remaining events occurred in the elderly cohort and included mild skin disorder (n=1), moderate allergic dermatitis (n=1), and moderate allergic pruritis (n=1); all considered related to study drug.

There were 2 subjects (1 elderly, 1 young adult) who had changes in laboratory values that were considered potentially clinically significant. One elderly subject (Subject 0001-11110) had a change in urine pH at end-of-study and one young adult (Subject 0001-11213) had a change in total bilirubin at end-of-study; both post-baseline values were not considered potentially clinically significant. Subject 0001-11110 also had two adverse events, moderate allergic pruritis and moderate rash.

One elderly subject (Subject 0001-1117) had an increase in systolic blood pressure (SBP) on Day 2 post-dose that was considered potentially clinically significant. The subject's SBP returned to within the reference range the following day.

One elderly subject (Subject 0001-1116) had a QTcB value on Day 3 that exceeded 500 msec when the baseline was <500 msec. Another follow-up electrocardiogram (ECG) was not performed, therefore it is not known whether the QTcB value returned to baseline, however, no adverse events reported for this subject. There were 2 elderly subjects and 1 young adult with abnormal post-baseline ECGs, but were not considered clinically significant.

No clinically significant change (known to have clinical sequelae) in laboratory (chemistry, hematology, and urinalysis), vital signs (other than blood pressure), and ECG findings was noted.

SPONSOR'S CONCLUSIONS: Following single 1-hour IV infusion of ceftaroline fosamil 600 mg in healthy elderly (≥65 years of age) and healthy young adult (18-45 years of age) subjects:

- Pharmacokinetics of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 were modestly altered in healthy elderly subjects versus healthy young adults.
- C_{max} of ceftaroline fosamil, ceftaroline, and M-1 were relatively unchanged, while AUC_{0-t} or $AUC_{0-\infty}$ were 12%, 33%, and 48% higher, respectively, in elderly subjects than young adults.
- Modestly higher $AUC_{0-\infty}$ for ceftaroline and M-1 in the older cohort could largely be explained by decreased renal function in healthy elderly subjects relative to that in healthy young adults.
- Dosage adjustment for elderly subjects, beyond that recommended for impaired renal function, is not likely necessary.
- Ceftaroline fosamil was well-tolerated in healthy young adults and in healthy elderly subjects ≥65 and ≥75 years of age.
- Elderly subjects had a higher incidence of adverse events and abnormal laboratory, vital signs, and ECG findings, but none were considered clinically significant.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

STUDY NO.: P903-15

Pharmacokinetics of a single dose of ceftaroline in subjects 12 to 17 years of age receiving antibiotic therapy

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Date(s): 29 Apr 2008 – 12 Feb 2009
Investigator(s)/Clinical Site(s): JL Blumer, MD, PhD; University Hospitals Case Medical Center, Cleveland, OH
B Congeni, MD; Children's Hospital Medical Center of Akron, Akron, OH
C Moran, MD; Duke University Medical Center, Durham, NC
JE Sullivan, MD; University of Louisville, Louisville, KY
Analytical Site(s): [redacted] (b) (4)

OBJECTIVE:

- To evaluate the single-dose pharmacokinetic profile of ceftaroline administered by IV infusion of ceftaroline fosamil in subjects 12 to 17 years of age (inclusive) at a dose of 8 mg/kg for subjects weighing <75 kg or 600 mg for subjects weighing ≥75 kg
- To evaluate the safety of a single dose of ceftaroline fosamil administered by IV infusion in subjects 12 to 17 years of age (inclusive) at a dose of 8 mg/kg for subjects weighing <75 kg or 600 mg for subjects weighing ≥75 kg

METHODS

Study Design: P903-15 was a multi-center, open-label, non-comparative, single-dose (as below) study in adolescent subjects 12-17 years of age (n=10, for goal n=8), who were hospitalized and receiving antibiotic therapy for treatment of infections of any type.

- <75 kg: 8 mg/kg ×1 (1-hour IV infusion)
- ≥75 kg: 600 mg ×1 (1-hour IV infusion)

Inclusion Criteria: Males and females (using effective method of birth control), 12-17 years of age (inclusive), hospitalized and receiving antibiotic therapy for treatment of an infection of any type, ≥34 kg in weight, ≤30 kg/m^2 in body mass index (BMI), and creatinine clearance (CrCL) >80 mL/min by Schwartz formula (as below) were enrolled.

- For males ≤13 years and females 12-17 years:
  CrCL (in mL/min) = 0.55 × Height (in cm) / SCr (in mg/dL)
- For males 14-17 years:
  CrCL (in mL/min) = 0.70 × Height (in cm) / SCr (in mg/dL)

Treatment: Ceftaroline fosamil was administered as a single 8 mg/kg IV dose over 1 hour. Powder containing ceftaroline fosamil and L-arginine (excipient) was reconstituted with Sterile Water for Injection, and then transferred into an infusion bag/bottle of 250 mL of 0.9% sodium

chloride solution. The prepared infusion bag/bottle was stored at 2-8 ºC for no longer than 24 hours and used within 6 hours after removal from refrigerated storage.

Probenecid was prohibited from 3 days prior to dosing until 24 hours after study drug administration. Permitted concomitant medications were held during infusion of study drug. Subjects were to refrain from ingesting foods and beverages other than standardized meals, snacks, and beverages on Study Day until all pharmacokinetic samples were collected; alcohol-containing foods, beverages, or medications were prohibited from 48 hours prior to dosing. Subjects were also to refrain from drinking fluids during study drug administration and for at least 1 hour after completion of study drug administration.

Sample Collection: Plasma and urine samples were collected (**Table 1**) and analyzed for pharmacokinetic purposes.

Table 1. Pharmacokinetic sampling scheme for single 1-hour IV infusion of ceftaroline fosamil 8 mg/kg

Plasma	• Pre-dose • 30, 55 (within 5 min before end of infusion), and 75 min, and 2, 3, 6, and 12 h AFTER START of infusion
Urine	• Pre-dose • 0-2, 2-6, and 6-12 AFTER START of infusion

Analytical Methods: Pharmacokinetic samples were analyzed for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 by validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays for plasma (Method 3; PRD-RPT-BDM-00077, 2009) and for urine (Method 4; PRD-RPT-BDM-00080, 2008) (**Table 2**).

Table 2. Bioanalytical results of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma and urine

Criterion	Ceftaroline fosamil	Ceftaroline	Ceftaroline M-1	Comments
PLASMA				
Range	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	0.05-20 µg/mL (1:10 dilution tested with 16 µg/mL)	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	Satisfactory
LLOQ	0.05 µg/mL	0.05 µg/mL	0.05 µg/mL	Satisfactory
Linearity	R^2 = 0.9959	R^2 ≥0.9986	R^2 = 0.989	Satisfactory
Accuracy	Within ±3.9%	Within ±5.3%	Within ±15.7%	Satisfactory
Precision	–	≤4.7 %CV	–	Satisfactory
Stability	• Study Dates: 29 Apr 2008 – 12 Feb 2009 • Analysis Dates: 14 May 2009 – 19 May 2009 • Stability: 526 days at -70 ºC			Satisfactory
URINE				
Range	0.5-5 µg/mL (1:5 dilution tested with 3.8 µg/mL)	0.5-50 µg/mL (1:19 dilution tested with 38 µg/mL)[a]	0.5-50 µg/mL (1:19 dilution tested with 38 µg/mL)[a]	Satisfactory
LLOQ	0.5 µg/mL	0.5 µg/mL	0.5 µg/mL	Satisfactory
Linearity	R^2 = 0.9932	R^2 ≥0.9968	R^2 ≥0.9976	Satisfactory
Accuracy	Within ±14.5%	Within ±8.7%	Within ±5.4%	Satisfactory
Precision	–	≤2.7 %CV	≤3.6 %CV	Satisfactory
Stability	• Study Dates: 29 Apr 2008 – 12 Feb 2009 • Analysis Dates: 6 May 2009 – 12 May 2009 • Stability: 469 days at -70 ºC			Satisfactory

[a] *Dilution integrity was evaluated further for ceftaroline and M-1 in urine during analysis for Study P903-15*

Pharmacokinetic Assessment: Pharmacokinetic parameters for ceftaroline fosamil, ceftaroline, ceftaroline M-1 were determined using non-compartmental methods. Since doses were expressed in terms of anhydrous, acetate-free ceftaroline fosamil (MW, 684.68), corrections were made to the dose when calculating parameters for ceftaroline (MW, 604.70; 0.883 × ceftaroline fosamil dose) and ceftaroline M-1 (MW, 622.72; 0.909 × ceftaroline fosamil dose). Parameters included the following:

- C_{max}, maximum observed plasma concentration
- AUC_{0-t}, area under the curve up to time corresponding to the last measurable concentration
- $AUC_{0-\infty}$, area under the curve from time 0 to infinity
- T_{max}, corresponding time of C_{max}
- $t_{1/2}$, elimination half-life
- CL, plasma clearance
- V_{ss}, steady-state volume of distribution
- V_z, volume of distribution of terminal phase
- Ae_{0-t}, cumulative amount of drug excreted during entire urine collection period from time 0 to time t
- CL_r, renal clearance

Statistical Methods: Descriptive statistics were provided for pertinent pharmacokinetic parameters.

RESULTS

Study Population: In total, 9 subjects were enrolled, of which 8 received the full dose. Subject 0003-15001 refused further infusion after receiving 80% of the total dose because of extravasation at the infusion site, and was subsequently excluded from pharmacokinetic analysis. Based on dose preparation instructions for ceftaroline fosamil according to body weight, median dose administered (excluding Subject 0003-15001) was 393.5 mg and ranged 320-600 mg; only 1 subject received 600 mg. Of those enrolled, there were 5 males and 4 females, and 6/9 were white, 2/9 black, and 1/9 classified as other. Mean age of subjects was 13.7 ± 1.8 years. Weight ranged 40.6-79.1 kg and BMI ranged 16.9-26.3 kg/m^2. When estimated by Schwartz equation, CrCL ranged 87.0-308.0 mL/min.

Using the Schwartz equation, CrCL was greatly overestimated for some adolescent subjects due to low serum creatinine (SCr) values. As such, the Reviewer estimated renal function as CrCL (in mL/min) or glomerular filtration rate (GFR) (in mL/min/1.73 m^2) using various equations including Cockcroft-Gault, the 4-variable equation from the Modification of Diet in Renal Disease Study (MDRD4), and the equation from the Chronic Kidney Epidemiology Collaboration (CKD-EPI) (**Table 3**). Of these, the CKD-EPI formula provided the least overestimated measure of renal function in adolescent subjects (**Table 4**). However, regardless of the various estimations, all subjects may be considered as having normal renal function.

Table 3. Various equations for estimation of renal function

Schwartz	**CrCL (in mL/min)** = Height (in cm) / SCr (in mg/dL) × (0.55 if male ≤13 years or female 12-17 years; 0.70 if male 14-17 years)
Cockcroft-Gault	**CrCL (in mL/min)** = ((140 - Age) × Wt) / (72 × SCr) × (0.85 if female)
MDRD4	**GFR (mL/min/1.73 m^2)** = $175 \times (SCr,std)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$ where SCr is serum creatinine measured with standardized assay
CKD-EPI	**GFR (mL/min/1.73 m^2)** $= 141 \times \min(SCr/\kappa,1)^{\alpha} \times \max(SCr/\kappa,1)^{-1\,209} \times (0.993)^{Age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$ where κ is 0.7 for females; 0.9 for males α is -0.329 for females; -0.411 for males $\min(SCr/\kappa,1)$ is the minimum value of SCr/κ versus 1 $\max(SCr/\kappa,1)$ is the maximum value of SCr/κ versus 1

Table 4. Comparative estimates of renal function for adolescent subjects

Subject	SCr (mg/dL)	Schwartz CrCL (mL/min)	Cockcroft-Gault CrCL (mL/min)	MDRD4 GFR (mL/min/1.73 m^2)	CKD-EPI GFR (mL/min/1.73 m^2)
0001-15003	0.4	308.0	340.6	287.0	175.9
0001-15004	0.5	166.7	155.7	285.0	191.3
0001-15005	0.5	173.3	170.7	235.2	165.0
0001-15007	0.8	141.3	149.1	130.7	133.2
0002-15002	0.5	170.5	155.6	174.5	147.4
0002-15003	0.7	124.1	123.8	111.6	128.3
0003-15001	0.8	121.0	141.1	134.5	135.1
0004-15001	0.7	119.7	101.2	113.1	129.2
0004-15002	1.0	85.2	61.4	95.0	99.3

Pharmacokinetics: Several protocol deviations with potential implications on pharmacokinetic results were identified (**Table 5**).

Table 5. Protocol deviations for single 1-hour IV infusion of ceftaroline fosamil in adolescent subjects

Deviation	N	Comment
Dosing		
Incomplete infusion	1	Acceptable • Only 80% of total dose administered due to extravasation at infusion site • Subject excluded from pharmacokinetic analysis
Sampling – Plasma		
Sampling time deviation	1-2 occurrences in 6/8 subjects	Acceptable • Actual sampling times used in pharmacokinetic analysis
Sampling – Urine		
Sample not received or discarded	1-2 samples in 4/8 subjects	Acceptable • Results missing for following subjects: 0001-15004: 2-6 h 0001-15005: 0-2, 2-6 h 0001-15007: 2-6 h 0004-15002: 6-12 h • Amount recovered in urine underestimated

Pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in healthy elderly and healthy young adult subjects are listed in **Table 6**. Concentration-time profiles of ceftaroline and ceftaroline M-1 are displayed in **Figures 1** and **2**, respectively.

One subject (Subject 0004-15002) had unusually low plasma concentrations of ceftaroline fosamil and ceftaroline and unusually high concentrations of M-1. Prodrug C_{max} and AUC_{0-t} for Subject 0004-15002 was 9% and 8%, respectively, of the mean value for all other subjects, while ceftaroline C_{max} and $AUC_{0-\infty}$ was 18% and 14%, respectively. For M-1, C_{max} and $AUC_{0-\infty}$ for Subject 0004-15002 were 6.6 and 3.5 times, respectively, the mean value for all others subjects. Excluding this subject, there were no pharmacokinetic parameters with coefficient of variation (%CV) >50% except C_{max} and AUC_{0-t} for ceftaroline fosamil, and T_{max} and Ae_{0-t} for M-1.

Table 6. Mean ± SD pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 following single 1-hour IV infusions of ceftaroline fosamil 8 mg/kg in adolescents receiving antibiotics

Parameter	**Adolescents (Subject 0004-15002 Excluded)[b] 8 mg/kg (n=7)** P903-15	**Adults 600 mg (n=6)** P903-01
Ceftaroline fosamil		
C_{max} (µg/mL)	3.69 ± 3.41	3.44 ± 1.18
T_{max} (h)[a]	0.50 (0.48-0.92)	0.33 (0.33-0.67)
AUC_{0-t} (µg*h/mL)	2.59 ± 2.52	3.53 ± 2.31
Ceftaroline		
C_{max} (µg/mL)	17.03 ± 3.63	18.97 ± 0.71
T_{max} (h)[a]	0.95 (0.48-1.00)	1.00 (0.92-1.25)
AUC_{0-t} (µg*h/mL)	43.05 ± 9.92	55.31 ± 8.94
$AUC_{0-\infty}$ (µg*h/mL)	43.57 ± 10.11	56.79 ± 9.31
$t_{1/2}$ (h)	1.86 ± 0.17	1.60 ± 0.38
V_{ss} (L)	25.27 ± 7.13	–
V_z (L)	19.74 ± 6.05	21.97 ± 5.43
CL (L/h)	9.36 ± 2.15	9.58 ± 1.85
CL_r (L/h)	4.95 ± 1.69	*(results underestimated)*
Ae_{0-t} (% of dose)	54.76 ± 18.49	*(results underestimated)*
Ceftaroline M-1		
C_{max} (µg/mL)	1.25 ± 0.52	2.72 ± 0.77
T_{max} (h)[a]	1.30 (0.92-3.00)	1.00 (0.67-5.00)
AUC_{0-t} (µg*h/mL)	7.63 ± 1.29	12.88 ± 2.51
$AUC_{0-\infty}$ (µg*h/mL)	8.47 ± 1.57	15.80 ± 3.21
$t_{1/2}$ (h)	3.41 ± 0.39	3.50 ± 1.36
V_{ss} (L)	240.57 ± 53.55	–
V_z (L)	244.8 ± 58.9	177.1 ± 60.5
CL (L/h)	49.13 ± 10.18	35.63 ± 6.60
CL_r (L/h)	2.15 ± 0.94	*(results underestimated)*
Ae_{0-t} (% of dose)	4.35 ± 2.28	*(results underestimated)*

[a] *Reported as median (minimum-maximum)*
[b] *Outlier due to unusually low concentrations of ceftaroline fosamil and ceftaroline and unusually high concentrations of M-1*

Figure 1. Mean ±SD **ceftaroline** concentrations following single doses of ceftaroline fosamil 8 mg/kg (for <75 kg) or 600 mg (for ≥75 kg) as a 1-hour IV infusion in adolescents receiving antibiotics

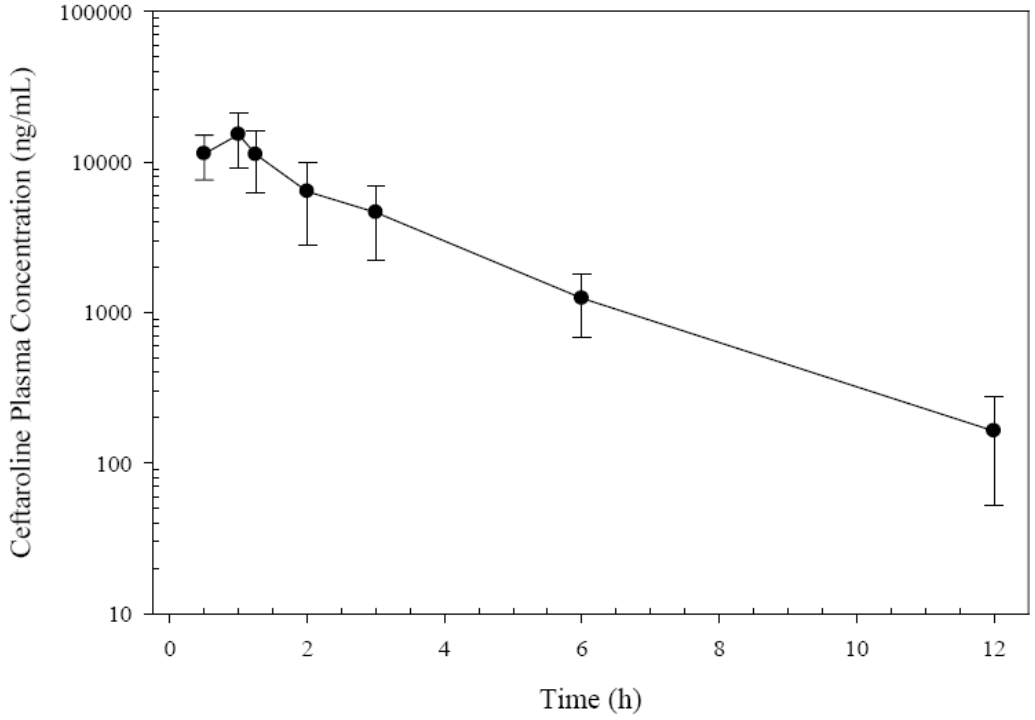
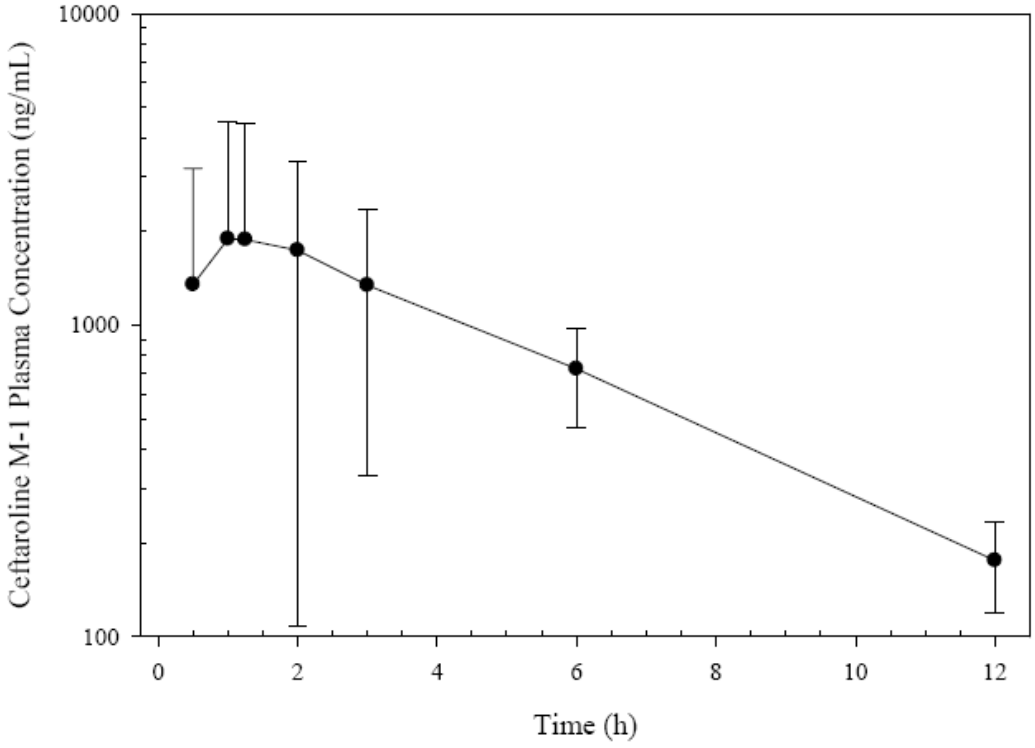


Figure 2. Mean ±SD **ceftaroline M-1** concentrations following single doses of ceftaroline fosamil 8 mg/kg (for <75 kg) or 600 mg (for ≥75 kg) as a 1-hour IV infusion in adolescents receiving antibiotics



Reviewer Comment: Plasma protein binding was not investigated in adolescent subjects, however any changes in protein binding is unlikely to have a significant impact on the fraction unbound as ceftaroline is minimally bound to plasma proteins (~20%).

(i) Ceftaroline fosamil (prodrug): Mean C_{max} and AUC_{0-t} of adolescent subjects (excluding outlier, Subject 0004-15002) were 3.69 µg/mL and 2.59 µg*h/mL, respectively, versus 3.44 µg/mL and 3.53 µg*h/mL for healthy adults following single 600 mg dose of ceftaroline fosamil from the single- and multiple-ascending dose study, P903-01. T_{max} expectedly occurred during the 1-hour IV infusion due to rapid conversion to active ceftaroline. Because of this rapid biotransformation, parameters like $AUC_{0-\infty}$, $t_{1/2}$, V_{ss}, CL could not be accurately calculated since the terminal phase of the prodrug could not be characterized. Unchanged ceftaroline fosamil was not detected in urine in any subject.

(ii) Ceftaroline (active metabolite): Mean ceftaroline C_{max} and $AUC_{0-\infty}$ of adolescent subjects (excluding outlier, Subject 0004-15002) were 10% and 23% lower, respectively, than healthy adults following single 600 mg dose of ceftaroline fosamil from Study P903-01 (**Figures 3** and **4**). T_{max} generally occurred around the end of 1-hour IV infusion, while mean $t_{1/2}$ was 1.86 hours. Mean ceftaroline CL and V_z were similar between adolescent subjects in Study P903-15 and healthy adults in Study P903-01. Approximately 55% of the dose of ceftaroline was excreted in urine, although results may be underestimated due to missing urine samples.

Reviewer Comment: Based on similar pharmacokinetics of ceftaroline following single doses, it appears the fixed adult dose of 600 mg would be appropriate for adolescent subjects (12-17 years old) to match exposures of active ceftaroline in healthy adults (≥18 years old). Further dose investigations by the Sponsor should also consider the pharmacokinetic/pharmacodynamic parameter, unbound %T>MIC.

(iii) Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline): Mean C_{max} and $AUC_{0-\infty}$ for M-1 in adolescent subjects (excluding outlier, Subject 0004-15002) were 54% and 46% lower, respectively, than healthy adults following single 600 mg dose of ceftaroline fosamil from Study P903-01 (**Figures 5** and **6**). T_{max} ranged 0.92-3.00 hours, while mean $t_{1/2}$ was 3.41 hours. Mean estimates of CL and V_z for ceftaroline M-1 were both 38% higher in adolescent subjects in Study P903-15 and healthy adults in Study P903-01. Approximately 4% of the dose of M-1 was excreted in urine, although results may be underestimated due to missing urine samples.

Figure 3. Individual **ceftaroline C_{max}** following single 1-h infusions of ceftaroline fosamil in adolescent subjects (12-17 years, n=8) versus healthy adults (≥18 years, n=6) from Study P903-01
*(*open triangle indicates outlier)*

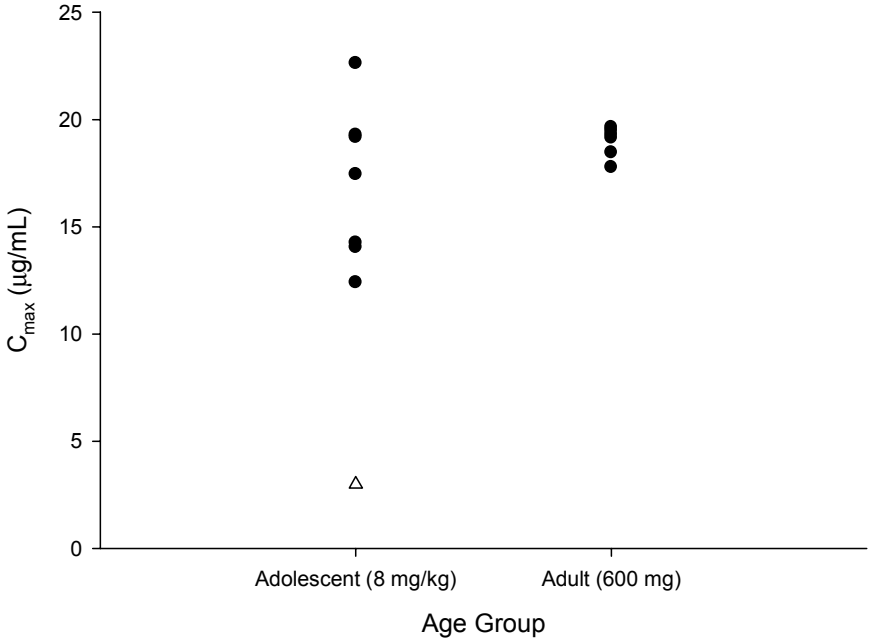


Figure 4. Individual **ceftaroline $AUC_{0-\infty}$** following single 1-h infusions of ceftaroline fosamil in adolescent subjects (12-17 years, n=8) versus healthy adults (≥18 years, n=6) from Study P903-01
*(*open triangle indicates outlier)*

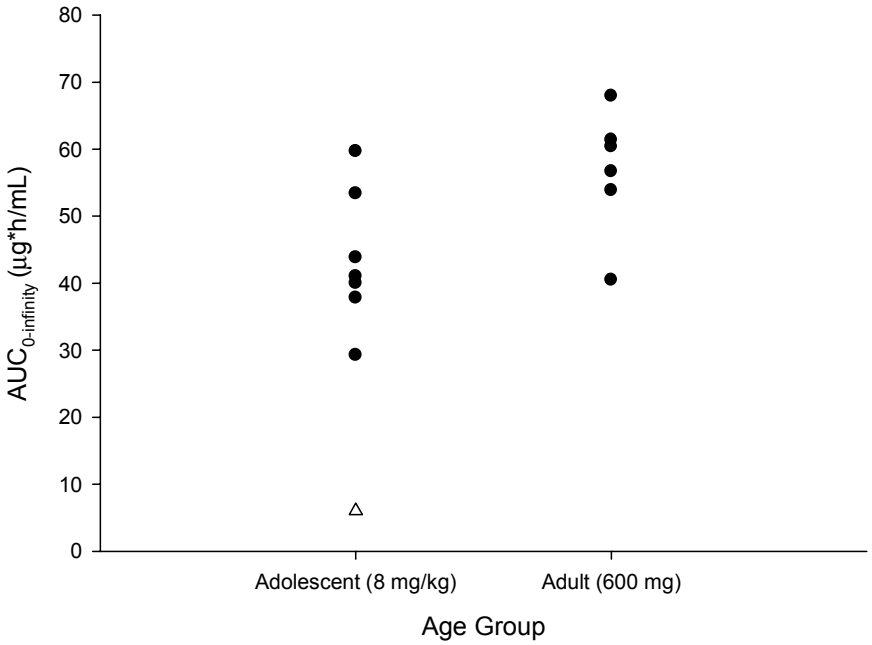


Figure 5. Individual **ceftaroline M-1 C_{max}** following single 1-h infusions of ceftaroline fosamil in adolescent subjects (12-17 years, n=8) versus healthy adults (≥18 years, n=6) from Study P903-01 *(*open triangle indicates outlier)*

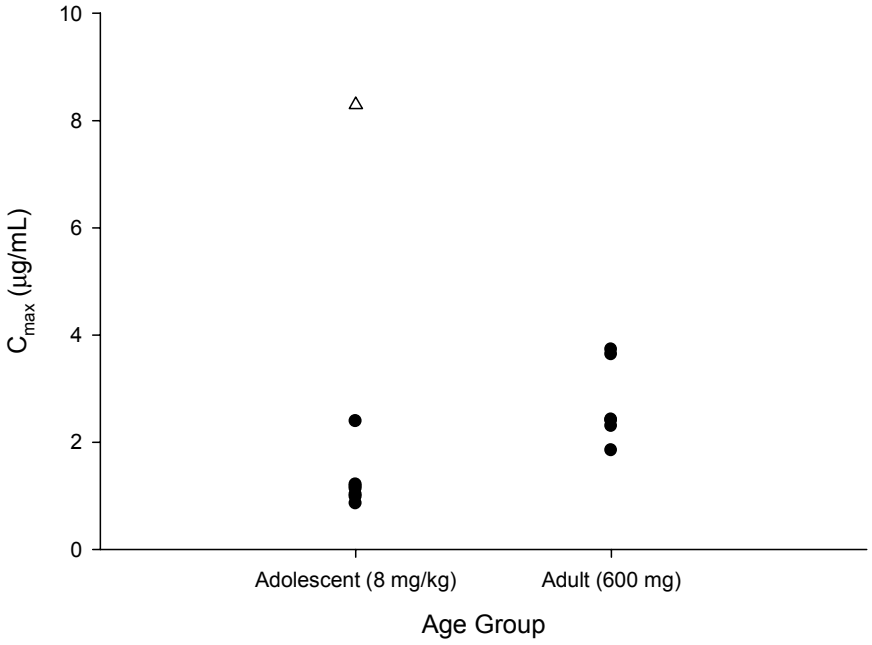
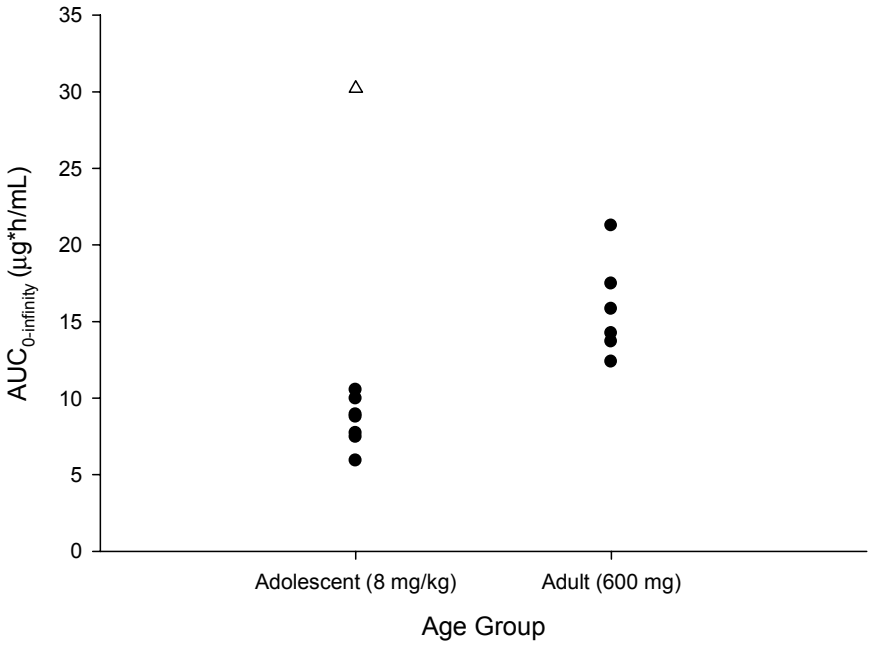


Figure 6. Individual **ceftaroline M-1 $AUC_{0-\infty}$** following single 1-h infusions of ceftaroline fosamil in adolescent subjects (12-17 years, n=8) versus healthy adults (≥18 years, n=6) from Study P903-01 *(*open triangle indicates outlier)*



Safety: In total, 8 adverse events were reported by 5/9 (56%) enrolled subjects, all of which were considered mild or moderate in severity. Of these, 3 events in 3/9 (33%) subjects were considered related to study drug: extrasystoles, vomiting, and prolonged QT interval (mild) on electrocardiogram (ECG). All events were resolved except for the case of prolonged QT interval that was ongoing at the final ECG assessment on Study Day 2. The subject's QTcB (corrected for heart rate using Bazzett's formula) and QTcF (corrected heart rate using Fridericia's formula) values were <450 msec and similar between pre- and post-dose measurements.

One event of infusion site extravasation led to discontinuation of study drug in one subject (Subject 0003-15001), who received 80% of the total dose. A serious adverse event of pathologic fracture of the humerus was also reported in this subject who was diagnosed with osteomyelitis. The fracture occurred 13 days after study drug administration, and was considered mild in severity and unrelated to study drug. Subject 0003-15001 also experienced arthralgia of the elbow on Study Day 13, which was moderate in severity and unrelated to study drug.

One subject had a hematology value that was considered potentially clinically significant: a long activated partial thromboplastin time (PTT) on Study Day 2 (91.0 sec) that was 127.5% above baseline (40.0 sec). However, the subject had suffered major trauma 7 days before study drug administration, and had received plasma, red blood cells, albumin, and platelets for blood loss from trauma and subsequent surgery. The long activated PTT was not associated with an adverse event and was not clinically significant.

One subject had low diastolic pressure on Study Day 2 (48 mmHg) versus baseline (66 mmHg) that was considered potentially clinically significant. However, the low diastolic pressure was not associated with an adverse event and was not clinically significant.

No clinically significant change (known to have clinical sequelae) in laboratory (chemistry, hematology, and urinalysis), vital signs, and ECG findings was noted.

SPONSOR'S CONCLUSIONS: Following single 1-hour IV infusion of ceftaroline fosamil 8 mg/kg for those <75 kg or 600 mg for those ≥75 kg in hospitalized adolescent (12-17 years of age) subjects receiving antibiotic therapy for treatment of infections of any type:

- Mean C_{max} and $AUC_{0-\infty}$ of ceftaroline in adolescent subjects were approximately 10% and 23% less, respectively, than values observed in adult subjects following single 600 mg dose of ceftaroline fosamil in Study P903-01.
- There was an outlier, Subject 0004-15002, who had unusually low plasma concentrations of ceftaroline fosamil and ceftaroline and unusually high plasma concentrations of M-1.
- As a result of slightly lower systemic exposure in adolescent subjects receiving 8 mg/kg (up to 600 mg) of ceftaroline fosamil compared with adult subjects receiving 600 mg, a modestly higher dose per kilogram should be considered for those aged 12-17 years.
- Ceftaroline fosamil was well-tolerated in hospitalized adolescent subjects receiving antibiotic therapy.
- Most abnormal laboratory, vital signs, and ECG findings were consistent with subjects' medical conditions; none were considered clinically significant.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results. The Sponsor has yet to provide a dose recommendation for pediatric patients <18 years of age in the draft label, but rather indicates that safety and effectiveness of pediatric patients has not been studied. Based on single-dose pharmacokinetic data, it appears the fixed adult dose of 600 mg would be at least appropriate for adolescent subjects.

On 4 Feb 2010, the Sponsor submitted a deferral request and pediatric plan to assess ceftaroline fosamil in the following pediatric groups as a Phase 4 commitment for both complicated skin and skin structure infections (cSSSI) and community-acquired bacterial pneumonia (CABP) indications:

- Adolescent: ≥12 years to <18 years
- Children: ≥24 months to <12 years
- Infants/Toddlers: ≥28 days to <24 months
- Neonates: 0 days to <28 days (preterm and term)

(b) (4)

STUDY NO.: P903-18

An open-label pharmacokinetic, safety, and tolerability study of single intravenous doses of ceftaroline in subjects with end-stage renal disease (ESRD) on intermittent hemodialysis and subjects with normal renal function

Ceftaroline fosamil (prodrug)	TAK-599, PPI-0903
Ceftaroline (active metabolite of prodrug)	M-I, T-91825, PPI-0903M
Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline)	M-II, T-289079, PPI-0903M-1

Date(s): 18 Oct 2007 – 31 Jan 2008
Investigator(s): T Marbury, MD
Clinical Site(s): Orlando Clinical Research Center, Orlando, FL
Analytical Site(s): (b) (4)

OBJECTIVE:
- To determine the safety, tolerability, and pharmacokinetic profile of a single IV dose of ceftaroline fosamil in subjects with ESRD on intermittent hemodialysis and in subjects with normal renal function
- To determine the clearance of ceftaroline by hemodialysis

METHODS
Study Design: P903-18 was a single-center, open-label, parallel-group, single-dose study in subjects with normal renal function or with ESRD requiring intermittent hemodialysis (HD) (n=12, total). Creatinine clearance (CrCL) was estimated with Cockcroft-Gault and subjects were enrolled into the following renal function cohorts:
- Normal renal function (n=6): CrCL >80 mL/min
- ESRD (n=6): On intermittent HD 3-4 times/week

ESRD subjects on HD received a single IV dose of ceftaroline fosamil 400 mg as a 1-hour infusion once before HD (infusion completed 4 hours before HD) and once after HD (infusion started at least 1 hour after end of HD) with at least a 7-day washout period in between. HD sessions were 4 hours long in duration.

Inclusion Criteria: Males or females (using effective method of birth control) with normal renal function or ESRD requiring intermittent HD (same HD regimen for at least 1 month prior), 18-75 years of age, and 18-38 kg/m^2 (inclusive) in body mass index (BMI) were enrolled. Subjects in the normal renal function group were matched as closely as possible for the ranges of age and weight and the ratio of gender with ESRD subjects on HD.

Treatment: Ceftaroline fosamil was administered as a single 400 mg IV dose over 1 hour. Powder containing ceftaroline fosamil and L-arginine (excipient) was reconstituted with Sterile Water for Injection, and then transferred into an infusion bag/bottle of 250 mL of 0.9% sodium chloride solution. The prepared infusion bag/bottle was stored at 2-8 ºC for no longer than 24 hours and used within 6 hours after preparation.

For subjects with normal renal function, medications including over-the-counter medications and vitamin or herbal supplements were prohibited from 14 days prior to dosing, while hormonal drug products were prohibited from 30 days prior to dosing. For ESRD subjects, necessary concomitant medications were allowed except when excluded by name or pharmacologic class; immunosuppressive medications were specifically prohibited.

Standardized meals, appropriate for subjects' renal impairment, were provided during confinement. Subjects were required to abstain from alcohol within 72 hours before and caffeine or grapefruit-containing products within 48 hours before Study Day.

Sample Collection: Plasma, urine, and dialysate fluid samples were collected (**Table 1**) and analyzed for pharmacokinetic purposes.

Table 1. Pharmacokinetic sampling scheme for single 1-hour IV infusion of ceftaroline fosamil 400 mg

Subjects with Normal Renal Function	
Plasma	• Pre-dose • 20, 40, and 60 (immediately before end of infusion), 65, and 75 min, and at 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 h AFTER START of INFUSION
Urine	• Pre-dose • 0-2, 2-4, 4-8, 8-12, 12-24, and 24-48 h AFTER START of INFUSION
ESRD Subjects, Dose PRE-HD	
Plasma	• Pre-dose • 20, 40, and 60 (immediately before end of infusion), 65, and 75 min, and at 1.5, 2, 3, 5 (before HD), 9 (after HD), 12, 18, 24, 36, and 48 h AFTER START of INFUSION • 15 min, and 1, 2, 3, and 4 h AFTER START of HD (from dialyzer)
Dialysate	• 0-1, 1-2, 2-3, and 3-4 h AFTER START of HD
ESRD Subjects, Dose POST-HD	
Plasma	• Pre-dose • 20, 40, and 60 (immediately before end of infusion), 65, and 75 min, and at 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, and 72 h AFTER START of INFUSION

Analytical Methods: Pharmacokinetic samples were analyzed for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 by validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays for plasma (Method 3; PRD-RPT-BDM-00077, 2009) and for urine and (partially validated) dialysate (Method 4; PRD-RPT-BDM-00080, 2008) (**Table 2**).

Table 2. Bioanalytical results of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in plasma, urine, and dialysate fluid

Criterion	Ceftaroline fosamil	Ceftaroline	Ceftaroline M-1	Comments
PLASMA				
Range	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	0.05-20 µg/mL (1:10 dilution tested with 16 µg/mL)	0.05-10 µg/mL (1:10 dilution tested with 8 µg/mL)	Satisfactory
LLOQ	0.05 µg/mL	0.05 µg/mL	0.05 µg/mL	Satisfactory
Linearity	R^2 ≥0.9934	R^2 ≥0.9963	R^2 ≥0.9882	Satisfactory
Accuracy	Within ±5.6%	Within ±9.2%	Within ±12.6%	Satisfactory
Precision	≤3.2 %CV	≤2.8 %CV	≤4.2 %CV	Satisfactory
Stability	• Study Dates: 18 Oct 2007 – 31 Jan 2008 • Analysis Dates: 19 Feb 2008 – 17 Mar 2008 • Stability: 526 days at -70 ºC			Satisfactory
URINE				
Range	0.5-5 µg/mL (1:5 dilution tested with 3.8 µg/mL)	0.5-50 µg/mL (1:9 dilution tested with 38 µg/mL)[a]	0.5-50 µg/mL (1:5 dilution tested with 38 µg/mL)	Satisfactory
LLOQ	0.5 µg/mL	0.5 µg/mL	0.5 µg/mL	Satisfactory
Linearity	R^2 = 0.9957	R^2 ≥0.9944	R^2 ≥0.9923	Satisfactory
Accuracy	Within ±2.8%	Within ±5.5%	Within ±11.2%	Satisfactory
Precision	≤7.0 %CV	≤3.4 %CV	≤5.6 %CV	Satisfactory
Stability	• Study Dates: 18 Oct 2007 – 31 Jan 2008 • Analysis Dates: 14 Feb 2008 – 14 Mar 2008 • Stability: 469 days at -70 ºC			Satisfactory
DIALYSATE				
Accuracy	Within ±15.7%	Within ±14.1%	Within ±7.5%	Satisfactory
Stability	• Study Dates: 18 Oct 2007 – 31 Jan 2008 • Analysis Dates: 28 Feb 2008 – 29 Feb 2008 • Stability: 469 days at -70 ºC for urine			Satisfactory

[a] *Dilution integrity was evaluated further for ceftaroline in urine during analysis for Study P903-18*

Pharmacokinetic Assessment: Pharmacokinetic parameters for ceftaroline fosamil, ceftaroline, ceftaroline M-1 were determined using non-compartmental methods. Since doses were expressed in terms of anhydrous, acetate-free ceftaroline fosamil (MW, 684.68), corrections were made to the dose when calculating parameters for ceftaroline (MW, 604.70; 0.883 × ceftaroline fosamil dose) and ceftaroline M-1 (MW, 622.72; 0.909 × ceftaroline fosamil dose). Parameters included the following:

- C_{max}, maximum observed plasma concentration
- $AUC_{0\text{-}t}$, area under the curve up to time corresponding to the last measurable concentration
- $AUC_{0\text{-}\infty}$, area under the curve from time 0 to infinity
- T_{max}, corresponding time of C_{max}
- $t_{1/2}$, elimination half-life
- CL, plasma clearance
- V_{ss}, steady-state volume of distribution
- $Ae_{0\text{-}t}$, cumulative amount of drug excreted during entire urine collection period from time 0 to time t
- CL_r, renal clearance
- Extraction ratio
  $= (C_{p,arterial} - C_{p,venous}) / C_{p,arterial}$

where $C_{p,arterial}$ and $C_{p,venous}$ are plasma concentrations entering (arterial blood) and leaving (venous blood) dialyzer, respectively

- CL_D, plasma clearance by dialysis

  $CL_D = Q_B (1\text{-Hct}) ((C_{p,in} - C_{p,out}) / (C_{p,in}))$

  where Q_B is blood flow rate entering dialyzer, Hct is hematocrit, and $C_{p,in}$ and $C_{p,out}$ are plasma concentrations entering and leaving dialyzer

  — or —

  $CL_D = DAe_{0\text{-t,dialysis}} / AUC_{0\text{-t,dialysis}}$

  where $DAe_{0\text{-t,dialysis}}$ is amount of drug recovered in dialysate over entire dialysis period and $AUC_{0\text{-t,dialysis}}$ is AUC over entire dialysis period

Statistical Methods: Pharmacokinetic parameters for subjects with normal renal function and ESRD dosed before and after HD were compared using Statistical Analysis System (SAS) Version 9.1.3. The paired difference between each ESRD subject and the matched subject with normal renal function in log-transformed C_{max}, $AUC_{0\text{-t}}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, and CL was analyzed using the one-sample t-test, while T_{max} was analyzed using the Wilcoxon Signed-Rank test. The 90% confidence interval (CI) was constructed for the geometric mean ratio for C_{max}, $AUC_{0\text{-t}}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, and CL between ESRD subjects and matched normal subjects.

RESULTS

Study Population: In total, 12 subjects were enrolled, and subjects with normal renal function were well matched to those with ESRD on HD by age, gender, and weight as intended. Mean ± SD age was 47.3 ± 8.2 and 48.3 ± 6.9 years, respectively, for normal and ESRD renal groups. Subjects in the normal group were 5/6 white and 1/6 black, while the ESRD group consisted of 3/6 white and 3/6 black; all study subjects were male. Weight ranged 69.9-117.7 kg across renal cohorts, with 89.7 ± 13.6 and 93.2 ± 18.2 kg for normal and ESRD groups, respectively. BMI ranged 22.9-35.6 kg/m^2 across renal cohorts, with 27.8 ± 3.9 and 29.8 ± 5.2 kg/m^2 for normal and severe groups, respectively. For subjects with normal renal function, CrCL ranged 101.4-168.9 mL/min.

Pharmacokinetics: Pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in subjects with normal renal function and ESRD subjects dosed pre-HD and post-HD are listed in **Table 3**. Concentration-time profiles of ceftaroline and ceftaroline M-1 are displayed in **Figures 1** and **2**, respectively. There were no pharmacokinetic parameters with coefficient of variation (%CV) >50% except for ceftaroline fosamil (up to 150% CV) due to its rapid bioconversion to active ceftaroline, making determination of certain parameters difficult.

Reviewer Comment: Plasma protein binding was not investigated in ESRD subjects, however, any changes in protein binding with renal impairment is unlikely to have a significant impact on the fraction unbound as ceftaroline is minimally bound to plasma proteins (~20%).

(i) Ceftaroline fosamil (prodrug): Concentrations of the prodrug were markedly higher in ESRD subjects, whether dosed pre- or post-HD, as mean C_{max} and $AUC_{0\text{-t}}$ values were 30-157 times that of subjects with normal renal function. Geometric mean ratios for C_{max}, $AUC_{0\text{-t}}$, and $AUC_{0\text{-}\infty}$ were expressed with wide 90% CI ranges due to high inter-subject variability for ceftaroline fosamil. T_{max} expectedly occurred during the 1-hour IV infusion in all groups due to

rapid conversion to active ceftaroline. Because of this rapid biotransformation, parameters like $AUC_{0-\infty}$, $t_{1/2}$, V_{ss}, and CL could not be accurately calculated for all subjects since the terminal phase of the prodrug could not be characterized.

Reviewer Comment: The Sponsor indicates plasma concentrations of ceftaroline fosamil were only markedly higher in ESRD subjects during the 1-hour infusion period, after which concentrations were similar between groups. The Sponsor postulates that higher prodrug concentrations were likely due to the same arm being reserved for IV infusion and pharmacokinetic sampling in ESRD subjects, while the opposing arm was used for HD. Only prodrug concentrations are anticipated to be affected by the use of the same arm for both dosing and sampling as neither ceftaroline nor ceftaroline M-1 is directly infused.

ESRD subjects were anuric throughout the collection period, therefore CL_r and Ae_{0-t} could not be calculated for these subjects. For those with normal renal function, ceftaroline fosamil was not detected in urine. The prodrug was also undetected in dialysate fluid of ESRD subjects dosed pre-HD.

(ii) Ceftaroline (active metabolite): Ceftaroline $AUC_{0-\infty}$ was significantly greater in ESRD subjects than in those with normal renal function, with geometric mean ratios of 1.89 when dosed pre-HD and 2.67 when dosed post-HD. Mean $AUC_{0-\infty}$ in ESRD subjects was 28% lower when dosed pre-HD than when dosed post-HD, indicating removal of ceftaroline by the HD procedure. C_{max} was less affected (particularly when dosed pre-HD), with geometric mean ratios of 1.05 and 1.74 for ESRD subjects dosed pre- and post-HD, respectively. T_{max} generally occurred around the end of 1-hour IV infusion and did not differ between groups. V_{ss} also appeared unchanged between groups, while mean CL in the ESRD cohort dosed pre- or post-HD was nearly one-half to one-third that of the normal renal cohort. Accordingly, mean $t_{1/2}$ in ESRD subjects (~6 hours) was approximately 2 times that of those with normal renal function (~3 hours).

Reviewer Comment: It is unclear why ceftaroline C_{max} values were greater when dosed post- versus pre-HD for all ESRD subjects. However, this discrepancy is unlikely to affect final dosing recommendations for ESRD.

ESRD subjects were anuric throughout the collection period, therefore CL_r and Ae_{0-t} could not be calculated, while approximately 60% of the dose was excreted in urine as unchanged ceftaroline in those with normal renal function. Mean extraction ratio of ceftaroline during HD for ESRD subjects was 0.60 ± 0.08. Mean dialysis clearance was 3.81 ± 0.44 L/h, and an average of 21.6% (or 76.5 mg) of the administered dose of ceftaroline was removed by the HD procedure, based on amounts collected in dialysate fluid.

(iii) Ceftaroline M-1 (inactive, open-ring metabolite of ceftaroline): C_{max} and $AUC_{0-\infty}$ for M-1 were significantly greater in the ESRD group than the normal group (more so than ceftaroline), with geometric mean ratios of 1.79 and 3.31, respectively, when dosed pre-HD and 2.86 and 6.74, respectively, when dosed post-HD. Consequently, $AUC_{0-\infty}$ ratios to active ceftaroline (calculated by the Reviewer) were greater for the ESRD cohort, ranging 0.26-0.38 when dosed pre-HD and 0.40-0.67 when dosed post-HD versus 0.15-0.20 for the normal renal cohort. As

observed with mild, moderate, and severe renal impairment (from Studies P903-02 and P903-04), T_{max} of M-1 was delayed in ESRD subjects, occurring between 5-8 hours post-dose versus 2-4 hours for those with normal renal function (**Figure 3**).

Reviewer Comment: Occurrence of this higher and delayed peak in M-1 for renally impaired subjects is theorized as attributable to a combination of: 1) greater circulating concentrations of the active ceftaroline in impaired subjects, which translates to more ceftaroline available for conversion/degradation into the open-ring metabolite, M-1, and 2) longer elimination $t_{1/2}$ of M-1 versus ceftaroline that contributes to additional and delayed accumulation of M-1.

Similarly to ceftaroline, CL for M-1 was considerably lower in ESRD subjects dosed pre- or post-HD, as mean values were approximately one-third to one-sixth that of subjects with normal renal function. Accordingly, mean $t_{1/2}$ in ESRD subjects (~8 hours) was approximately 2 times that of the normal group (~4 hours). However, unlike ceftaroline, V_{ss} for M-1 appeared to be lower in ESRD subjects, as mean values were 70% and 35% that of the normal group when dosed pre- and post-HD, respectively.

ESRD subjects were anuric throughout the collection period, therefore CL_r and Ae_{0-t} could not be calculated for these subjects. For those with normal renal function, approximately 6% of the administered dose of M-1 was detected in urine. M-1 was undetected in dialysate fluid of ESRD subjects dosed pre-HD, and consequently, dialysate clearance could not be determined. However, mean $AUC_{0-\infty}$ in ESRD subjects dosed pre-HD was 2 times that of when dosed post-HD, which is suggestive of M-1 removal by the HD procedure. Mean extraction ratio of M-1 during HD for ESRD subjects was 0.55 ± 0.08.

Reviewer Comment: Detection of M-1 in dialysate fluid was limited by LLOQ of 0.5 µg/mL relative to collected dialysate volumes of 3000 mL.

Table 3. Mean ± SD pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 following single 1-hour IV infusions of ceftaroline fosamil 400 mg in subjects with normal renal function and ESRD dosed pre- and post-HD

Parameter	Renal Function						
	Normal 400 mg (n=6)	**ESRD 400 mg, Pre-HD (n=6)**	Geometric Mean Ratio (90% CI)	p-value	**ESRD 400 mg, Post-HD (n=6)**	Geometric Mean Ratio (90% CI)	p-value
Ceftaroline fosamil							
C_{max} (µg/mL)	1.92 ± 0.95	105.6 ± 157.9	8.26 (1.33-51.12)	0.0623	301.2 ± 320.1	60.45 (10.15-359.9)	0.0019
T_{max} (h)[a]	0.67 (0.33-0.97)	0.98 (0.33-0.98)	–	–	0.98 (0.67-0.98)	–	–
AUC_{0-t} (µg*h/mL)	1.53 ± 0.84	46.08 ± 67.53	6.59 (1.33-32.51)	0.0580	119.4 ± 113.6	32.73 (6.46-165.7)	0.0030
$AUC_{0-\infty}$ (µg*h/mL)	2.30 ± 1.27[b]	55.02 ± 71.44	9.76 (0.29-325.5)	0.2384	210.8 ± 115.3[b]	91.82 (16.92-498.3)	0.0160
$t_{1/2}$ (h)	0.23 ± 0.17[b]	0.17 ± 0.06	–	–	0.11 ± 0.04[b]	–	–
V_{ss} (L)	38.71 ± 26.21[b]	22.51 ± 16.86	–	–	0.43 ± 0.32[b]	–	–
CL (L/h)	205.1 ± 113.0[b]	90.84 ± 88.51	–	–	2.23 ± 1.22[b]	–	–
CL_r (L/h)	–	–	–	–	–	–	–
Ae_{0-t} (% of dose)	–	–	–	–	–	–	–
Ceftaroline							
C_{max} (µg/mL)	16.48 ± 3.36	17.41 ± 3.75	1.05 (0.84-1.32)	0.6965	29.10 ± 8.49	1.74 (1.36-2.23)	0.0023
T_{max} (h)[a]	0.98 (0.97-1.08)	0.98 (0.98-1.08)	–	–	0.98 (0.98-0.98)	–	–
AUC_{0-t} (µg*h/mL)	48.26 ± 9.07	90.94 ± 16.25	1.89 (1.55-2.29)	0.0001	127.8 ± 12.64	2.67 (2.29-3.13)	0.0001
$AUC_{0-\infty}$ (µg*h/mL)	48.63 ± 9.17	92.00 ± 15.88	1.89 (1.57-2.29)	0.0001	128.6 ± 12.68	2.67 (2.28-3.12)	0.0001
$t_{1/2}$ (h)	2.75 ± 0.22	6.12 ± 0.81	–	–	6.16 ± 0.81	–	–
V_{ss} (L)	21.30 ± 4.32	23.41 ± 6.66	–	–	20.69 ± 3.92	–	–
CL (L/h)	7.47 ± 1.35	3.94 ± 0.73	–	–	2.77 ± 0.28	–	–
CL_r (L/h)	4.55 ± 1.01	–	–	–	–	–	–
Ae_{0-t} (% of dose)	60.40 ± 5.98	–	–	–	–	–	–
Ceftaroline M-1							
C_{max} (µg/mL)	0.89 ± 0.15	1.63 ± 0.48	1.79 (1.41-2.26)	0.0012	2.64 ± 0.93	2.86 (2.21-3.71)	<0.0001
T_{max} (h)[a]	4.00 (2.00-4.00)	4.98 (4.98-5.07)	–	–	8.00 (6.00-8.00)	–	–
AUC_{0-t} (µg*h/mL)	8.41 ± 2.10	28.45 ± 6.34	3.41 (2.67-4.36)	<0.0001	59.38 ± 17.70	7.02 (5.32-9.27)	<0.0001
$AUC_{0-\infty}$ (µg*h/mL)	8.92 ± 2.13	29.31 ± 6.37	3.31 (2.61-4.20)	<0.0001	60.48 ± 17.39	6.74 (5.16-8.82)	<0.0001
$t_{1/2}$ (h)	4.15 ± 0.36	8.16 ± 0.71	–	–	8.23 ± 0.70	–	–
V_{ss} (L)	299.1 ± 67.29	208.4 ± 44.03	–	–	104.6 ± 27.29	–	–
CL (L/h)	42.95 ± 11.58	12.83 ± 2.36	–	–	6.36 ± 1.51	–	–
CL_r (L/h)	2.52 ± 0.54	–	–	–	–	–	–
Ae_{0-t} (% of dose)	5.84 ± 1.22	–	–	–	–	–	–

[a] *Reported as median (minimum-maximum)*
[b] *Data from n=2*

Figure 1. Mean ±SD **ceftaroline** concentrations following single doses of ceftaroline fosamil 400 mg as a 1-hour IV infusion in subjects with normal renal function and ESRD dosed pre- and post-HD

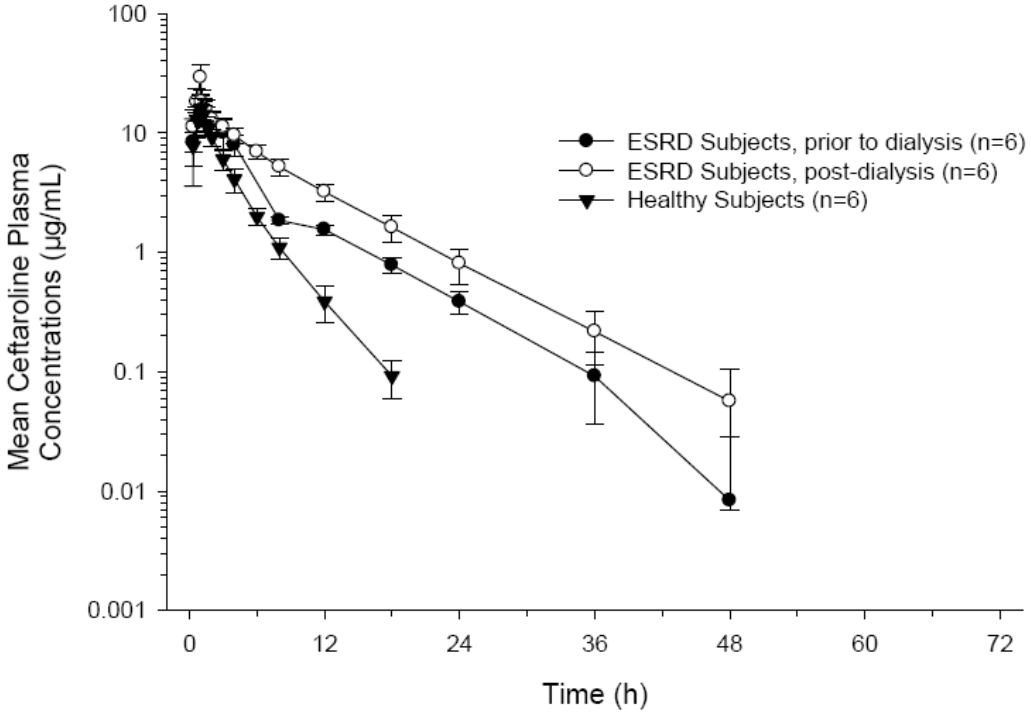


Figure 2. Mean ±SD **ceftaroline M-1** concentrations following single doses of ceftaroline fosamil 400 mg as a 1-hour IV infusion in subjects with normal renal function and ESRD dosed pre- and post-HD

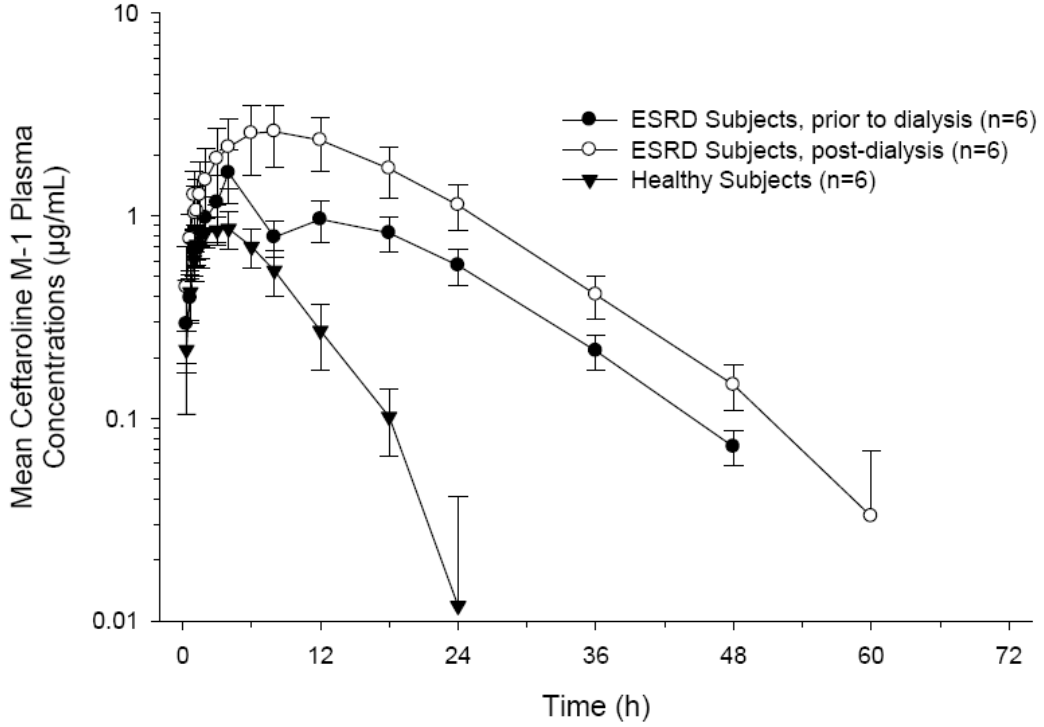
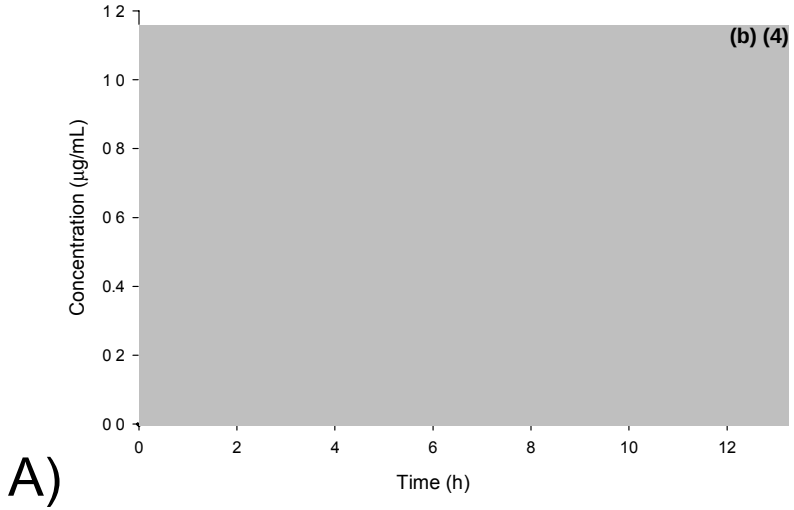
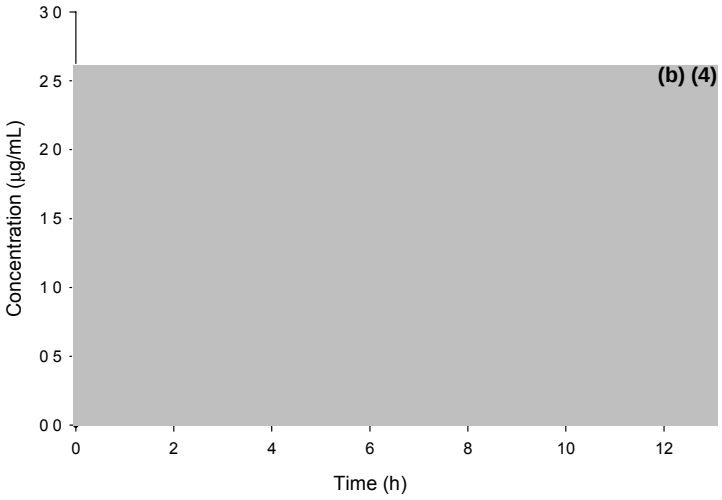


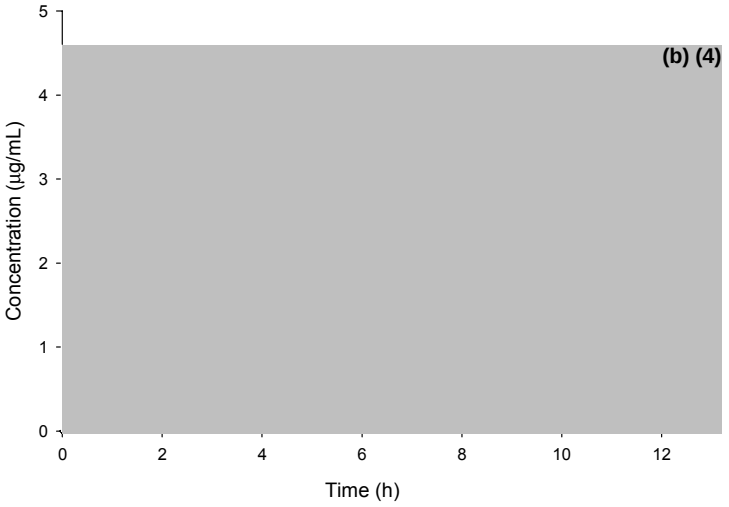
Figure 3. Individual **ceftaroline M-1** concentrations in **A)** subjects with normal renal function, and **B)** ESRD subjects dosed pre-HD, and **C)** ESRD subjects dosed post-HD following single 1-hour IV infusions of ceftaroline fosamil 400 mg



A)



B)



C)

Safety: In total, 4 adverse events were reported by 3/12 (25%) subjects: muscle spasms in the normal renal function cohort (n=1), graft thrombosis in the ESRD cohort dosed pre-HD (n=2), and nausea and vomiting in the ESRD cohort dosed post-HD (n=1). With the exception of severe intermittent vomiting, all events were classified as moderate in severity; none were considered related to study drug.

There were 5 instances of post-baseline abnormal values in blood pressure that were considered potentially clinically significant; all instances from 3 ESRD subjects. Two instances occurred in the pre-HD group: high systolic blood pressure (SBP) 4 hours after start of infusion and low SBP 24 hours after start of infusion. In the post-HD group, there were 3 instances: high SBP 4 hours after start of infusion, high diastolic blood pressure (DBP) 72 hours after start of infusion, and high DBP at end-of-study visit. The Sponsor indicates none of these abnormal values were unexpected, and consider changes in blood pressure common in subjects undergoing HD due to blood volume changes resulting from the procedure.

No clinically significant change in laboratory (chemistry, hematology, and urinalysis), vital signs (other than blood pressure), and electrocardiogram findings was noted.

SPONSOR'S CONCLUSIONS: Following single 1-hour IV infusion of ceftaroline fosamil 400 mg in subjects with normal renal function (CrCL mL/min) and subjects with ESRD on intermittent HD, dosed pre-HD (infusion completed 4 hours before HD) and post-HD (infusion started at least 1 hour after HD):

- Plasma concentrations of ceftaroline fosamil were markedly higher in ESRD subjects than in those with normal renal function during time of infusion, contributing to higher C_{max} and AUC_{0-t} values. (Higher concentrations considered likely due to the same arm used for pharmacokinetic sampling and IV dosing, while the other was reserved for HD.)
- Systemic exposures of active ceftaroline were significantly higher in ESRD subjects than in those with normal renal function, with geometric mean ratios of 1.74 for C_{max} and 2.67 for $AUC_{0-\infty}$ when dosed post-HD.
- Ceftaroline CL was on average 47% and 63% lower, respectively, in ESRD subjects dosed pre- and post-HD than the normal renal group.
- Systemic exposures of M-1 were significantly higher in the ESRD cohort, with geometric mean ratios of 2.86 for C_{max} and 6.74 for $AUC_{0-\infty}$ post-HD versus the normal cohort.
- M-1 CL was on average 70% and 85% lower, respectively, in the ESRD group dosed pre- and post-HD than the normal renal group.
- HD removed 21.6% of the administered dose of ceftaroline, as well as an estimated (but undetermined) amount of M-1.
- Ceftaroline fosamil was well-tolerated in subjects with normal renal function and ESRD subjects; safety profiles were similar between ESRD subjects dosed pre- and post-HD.
- ESRD subjects had a higher incidence of abnormal laboratory, vital signs, and electrocardiogram findings, but most were consequential to chronic conditions typical of ESRD subjects receiving HD.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results. In the draft labeling, the Sponsor indicates there is insufficient information to make specific dosage adjustment recommendations for patients with ESRD, including patients undergoing HD.

The Reviewer performed additional pharmacokinetic analyses to determine the appropriate dosing regimen of ceftaroline fosamil for ESRD subjects on intermittent HD versus subjects with normal renal function using data from Study P903-18. Plasma concentration-time data of active ceftaroline following single 1-hour IV infusions of ceftaroline fosamil 400 mg were fitted for each individual subject using WinNonlin software (version 5.2.1, Pharsight Corporation, Mountain View, CA). For ESRD subjects, data from when doses were administered post-HD were used to evaluate ceftaroline pharmacokinetics without the removal effect from HD procedure. A two-compartment IV infusion model with microconstants, no lag time, first-order elimination, and 1/y*y weighting was used. The model was selected based on visual inspection of fit and goodness of fit measured by the Akaike Information Criterion (AIC) and weighted R^2.

The ceftaroline-equivalent of the prodrug dose that was administered (0.883 × ceftaroline fosamil dose, or 353.2 mg) and actual infusion times were used. Only a few plasma samples deviated from scheduled times, so scheduled time points were used, and time points with zero concentration values after dose administration were omitted.

Once fitted, individual pharmacokinetic parameters were used to simulate ceftaroline fosamil regimens in subjects with normal renal function (n=6) and ESRD subjects when dosed post-HD (n=6) (**Table 4**). To check the accuracy of the 2-compartmental model, the Reviewer first simulated single 1-hour IV infusions of ceftaroline fosamil 400 mg (as done in Study P903-18), and compared simulated pharmacokinetic parameters of ceftaroline against those reported using the Sponsor's non-compartmental analysis (**Table 5**). Simulated results by the Reviewer were found to be similar to reported results by the Sponsor.

Table 4. Median (min-max) estimates of ceftaroline pharmacokinetic parameters used as input parameters for Reviewer simulations

Input Parameter	Normal Renal Function (n=6)	ESRD, Dose Post-HD (n=6)
V_1 (L)	16.93 (11.66-20.81)	6.30 (1.51-15.42)
K_{10} (1/h)	0.46 (0.42-0.54)	0.50 (0.18-2.09)
K_{12} (1/h)	0.15 (0.11-0.22)	5.25 (0.13-16.62)
K_{21} (1/h)	0.43 (0.38-0.46)	0.71 (0.34-2.77)

k_{10}, elimination rate constant; k_{12} and k_{21}, microtransfer rate constants between central and 2nd compartments; V_1, apparent volume of distribution of central compartment

Table 5. Ceftaroline pharmacokinetic parameters by Sponsor's non-compartmental analysis versus Reviewer's 2-compartmental analysis for subjects with normal renal function and ESRD following single 1-hour IV infusions of ceftaroline fosamil 400 mg

Normal Renal Function						
Subject No.	18201	18202	18203	18204	18205	18206
C_{max} (µg/mL)						
Sponsor	13.87	16.37	12.82	15.01	19.02	21.75
Reviewer	13.73	17.08	12.86	14.49	20.17	22.12
$AUC_{0-\infty}$ (µg*h/mL)						
Sponsor	43.34	47.43	37.92	43.54	60.65	58.92
Reviewer	42.19	45.39	37.02	41.84	58.88	56.23
$t_{1/2}$ (h)						
Sponsor	2.76	2.95	2.67	2.57	3.08	2.51
Reviewer	2.80	2.89	2.63	2.82	3.01	2.54
ESRD, Dose Post-HD						
Subject No.	18101	18102	18103	18104	18105	18106
C_{max} (µg/mL)						
Sponsor	44.31	21.07	26.40	33.02	23.00	26.83
Reviewer	28.46	19.92	17.38	29.39	19.94	22.30
$AUC_{0-\infty}$ (µg*h/mL)						
Sponsor	137.36	134.49	141.60	111.63	113.78	132.62
Reviewer	130.91	130.85	140.35	111.87	114.03	128.84
$t_{1/2}$ (h)						
Sponsor	5.00	6.25	7.30	5.51	6.64	6.27
Reviewer	4.83	6.18	6.91	5.01	6.48	6.15

Accuracy of the 2-compartmental model confirmed, the Reviewer then simulated steady-state exposures of active ceftaroline for the standard regimen (ceftaroline fosamil 600 mg Q12 × 3 days) in subjects with normal renal function and various renal-adjusted regimens (ceftaroline fosamil 200 mg Q12, 250 mg Q12, or 400 mg Q24 × 3 days) in ESRD subjects dosed post-HD. For Reviewer simulations, the ceftaroline-equivalent of the prodrug dose (0.883 × ceftaroline fosamil dose) was used and all doses were 1-hour IV infusions. Calculation of %*f*T>MIC (target pharmacokinetic/pharmacodynamic parameter) assumed equal protein binding between renal groups (20%) and was determined in 0.2-hour increments over the dosing interval.

Geometric mean of simulated C_{max} in the ESRD group was 47%, 34%, and 7% lower, respectively, with 200 mg Q12 (13.33 µg/mL), 250 mg Q12 (16.66 µg/mL), and 400 mg Q24 (23.34 µg/mL) regimens than the normal group (25.10 µg/mL) (**Figure 4**). Geometric mean of simulated AUC_{24} in the ESRD group was comparable with 200 mg Q12 (125.65 µg*h/mL) and 400 mg Q24 (125.70 µg*h/mL), while 13% greater with 250 mg Q12 (157.06 µg*h/mL) than the normal group (138.83 µg*h/mL) (**Figure 5**). Of simulated regimens, 200 mg Q12 was most suitable for ESRD subjects in matching ceftaroline AUC_{12} of the normal renal cohort across individual subjects. The regimen of 200 mg Q12 was favored over 400 mg Q24 in order to best maximize the time-dependent behavior of ceftaroline, and additionally, no significant level of exposure was further gained with the 250 mg Q12 regimen. Moreover, individual %*f*T>MIC curves over theoretical bacterial MICs for the 200 mg Q12 regimen in ESRD subjects dosed post-HD were comparable to or greater than that of the standard 600 mg Q12 regimen in subjects with normal renal function (**Figure 6**). Reviewer-simulated profiles of active ceftaroline following 600 mg Q12 × 3 days in subjects with normal renal function and 200 mg Q12 × 3 days in ESRD subjects dosed post-HD are shown in **Figure 7**.

Figure 4. Individual **ceftaroline C_{max} at steady-state** in subjects with normal renal function and ESRD subjects when dosed post-HD, **simulated by the Reviewer**

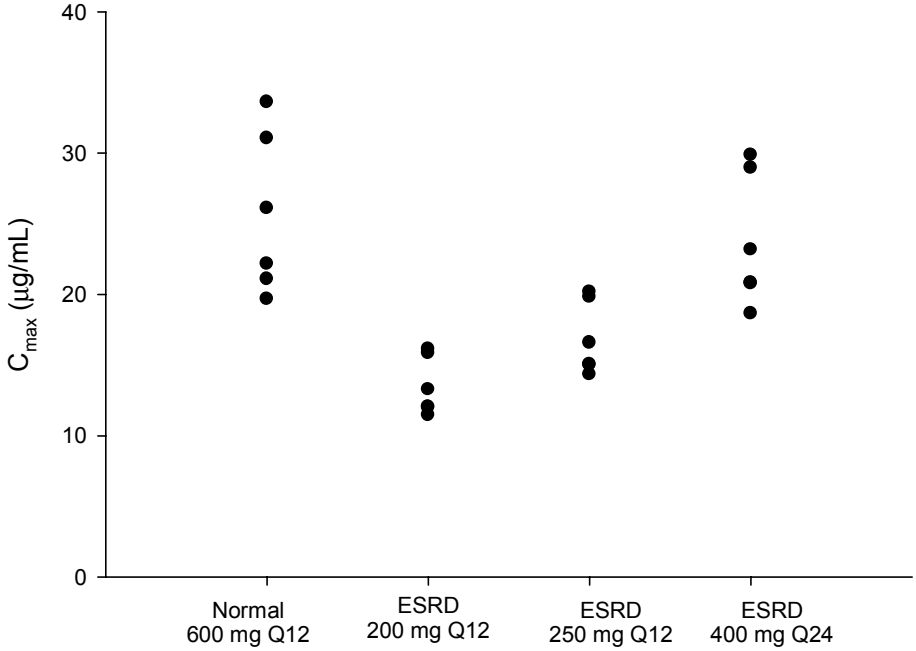


Figure 5. Individual **ceftaroline AUC_{24} at steady-state** in subjects with normal renal function and ESRD subjects when dosed post-HD, **simulated by the Reviewer**

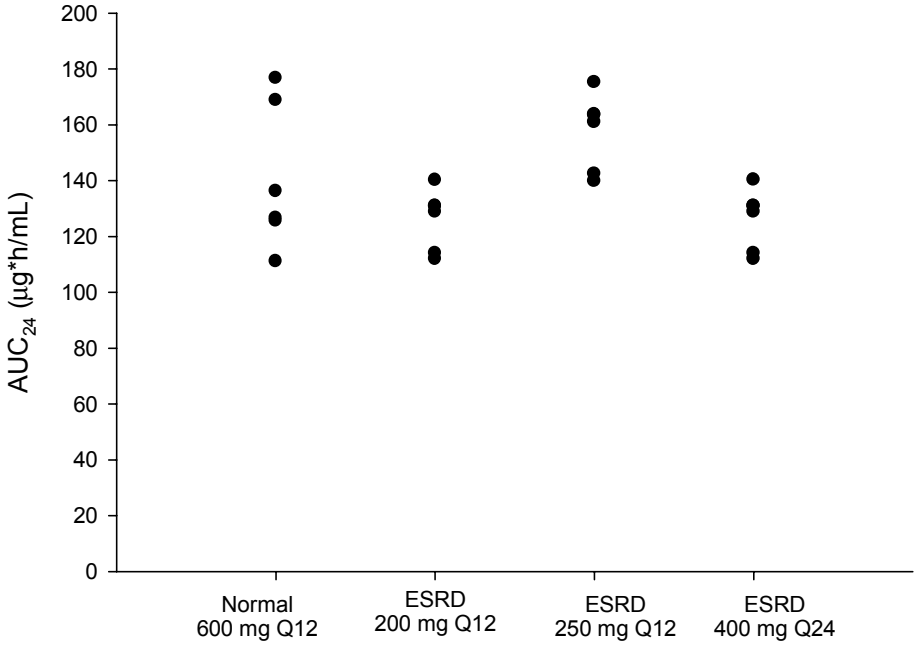


Figure 6. Individual **ceftaroline % *f*T>MIC at steady-state** in subjects with normal renal function and ESRD subjects when dosed post-HD, **simulated by the Reviewer**

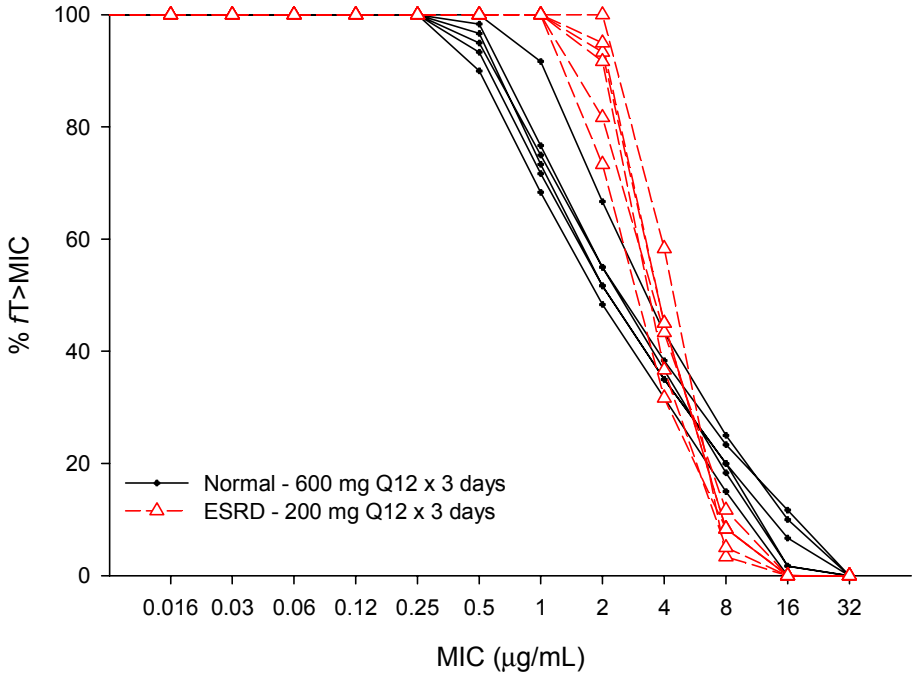
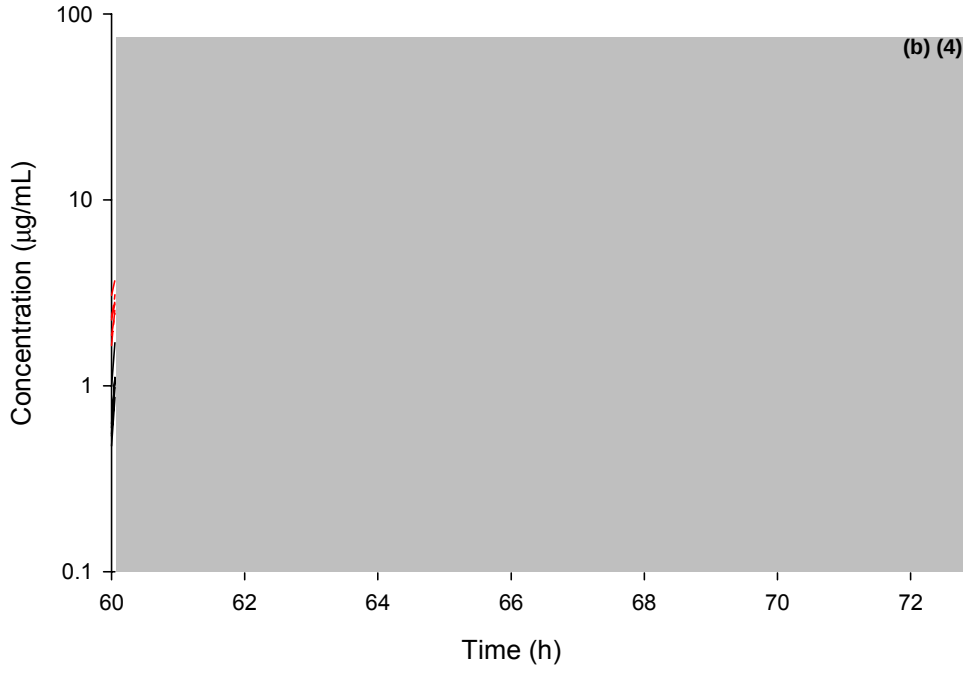


Figure 7. Individual **ceftaroline concentrations at steady-state** in subjects with normal renal function and ESRD subjects when dosed post-HD, **simulated by the Reviewer**



Based on Study P903-18 data, the renal-adjusted regimen of ceftaroline fosamil 200 mg Q12 appears to be appropriate for ESRD subjects dosed post-HD in matching ceftaroline exposures (as AUC and %*f*T>MIC) of the standard 600 mg Q12 regimen in subjects with normal renal function (CrCL >80 mL/min).

4.1.4 Extrinsic Factors

REPORT NO.: ICPD 00174-5

Assessment of the impact of concomitant medications administered to patients with either complicated skin and skin structure infections or community-acquired pneumonia on the pharmacokinetics of ceftaroline

Report Date: 30 Oct 2009
Investigator(s)/Institution(s): S Van Wart, SM Bhavnani, PG Ambrose, DK Reynolds
Institute for Clinical Pharmacodynamics, Ordway Research Institute, Inc., Latham, NY

OBJECTIVE: To evaluate the impact of concomitant medications administered to Phase 2/3 patients with either complicated skin and skin structure infections (cSSSI) or community-acquired pneumonia (CAP) on the pharmacokinetics of ceftaroline

METHODS

Analysis Design: ICPD 00174-5 was an exploratory population pharmacokinetic analysis that assessed changes in ceftaroline exposure for patients who received concomitant mediations using data supplied from five clinical trials in adult patients with cSSSI or CAP (**Table 1**). Phase 2/3 cSSSI and CAP patients treated with ceftaroline fosamil received 600 mg IV Q12 (adjusted to 400 mg IV Q12 for moderate renal impairment defined as creatinine clearance [CrCL] >30 and ≤50 mL/min) with doses administered as single 1-hour infusions or divided as two consecutive 0.5-hour infusions.

Table 1. Overview of Phase 2/3 studies in cSSSI and CAP included in concomitant medications analysis

Study No.	Ceftaroline N	Treatment	Sampling
cSSSI			
P903-03 *(Phase 2)*	67	Ceftaroline fosamil • 600 mg IV Q12 • Single 1-h infusions • For 7-14 days	Day 3 • Pre-dose • ±5 min after end of infusion • 1-3 h after end of infusion • 4-8 h after end of infusion
P903-06 *(Phase 3)*	353	Ceftaroline fosamil • 400 mg IV Q12 (CrCL >30 & ≤50 mL/min) • 600 mg IV Q12 (CrCL >50 mL/min) • Single 1-h infusions • For 5-14 days	
P903-07 *(Phase 3)*	348		
CAP			
P903-08 *(Phase 3)*	305	Ceftaroline fosamil • 400 mg (200 mg + 200 mg) IV Q12 (CrCL >30 & ≤50 mL/min) • 600 mg (300 mg + 300 mg) IV Q12 (CrCL >50 mL/min) • Two consecutive 0.5-h infusions • For 5-14 days	Day 1 • Pre-dose of 1st infusion • ±5 min after end of 1st infusion • 1-3 h after end of 2nd infusion • 4-8 h after end of 2nd infusion
P903-09 *(Phase 3)*	317		

Patients with cSSSI in the three Phase 2/3 trials received ceftaroline fosamil as a single 600 mg IV infusion over 1 hour followed by IV placebo infused over 1 hour every 12 hours. Patients in the comparator arm received vancomycin 1 g IV infused over 1 hour followed by aztreonam 1 g IV infused over 1 hour every 12 hours (aztreonam was discontinued if a gram-negative infection was not suspected or identified).

Patients with CAP in the two Phase 3 trials received ceftaroline fosamil as two consecutive 300 mg IV infusions over 0.5 hour every 12 hours to maintain study blind. Patients in the comparator arm received ceftriaxone 1 g IV over 0.5 hour followed by IV placebo over 0.5 hour every 24 hours and two consecutive placebo infusions, each infused over 0.5 hour every 24 hours, administered 12 hours after each dose of ceftriaxone + placebo.

Population Pharmacokinetic Models: Final population pharmacokinetic models for ceftaroline fosamil and ceftaroline were used to predict individual ceftaroline concentrations with Bayesian parameter estimates for the 12-hour dosing interval on the day of pharmacokinetic sampling for each patient. The maximum plasma concentration (C_{max}) of ceftaroline was determined by direct observation of individual predicted concentrations, while the area under the plasma concentration-time curve over 0-12 hours (AUC_{0-12}) for ceftaroline was calculated using the linear trapezoidal rule.

Final population pharmacokinetic models for ceftaroline fosamil and active ceftaroline were previously developed using NONMEM® Version 6 Level 2.0 and are reported/reviewed elsewhere in detail (Reports ICPD 00174-3 and ICPD 00174-4). In brief, ceftaroline fosamil and ceftaroline were modeled in sequential fashion by including Bayesian parameter estimates from the final model for ceftaroline fosamil as data variables within the NONMEM® analysis dataset for ceftaroline. Thus, the fraction of prodrug converted to ceftaroline (f_m) was not estimated but rather pharmacokinetic parameters were conditioned on f_m. The final model that best characterized plasma concentrations of the prodrug with IV dosing was a three-compartment model with zero-input and first-order elimination. The final model that best characterized plasma concentrations of active ceftaroline with IV dosing was a two-compartment model with first-order input (conversion of prodrug to ceftaroline) and both first-order and Michaelis-Menten elimination.

Concomitant Medications: Concomitant medications were categorized according to the following:

- substrates, inhibitors, and inducers of the cytochrome P450 enzyme system (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5/7)
- anionic or cationic drugs known to undergo active tubular secretion in the kidneys or alter renal blood flow
- drugs with vasodilatory or vasoconstrictive properties which could potentially impact renal blood flow and subsequently glomerular filtration rate

For each concomitant medication used, the generic name and/or brand name, actual dose amount, route of administration, and start/stop dates and times were recorded and utilized. Each generic medication was consolidated, as needed, to accommodate various dosage formulations, and drug combination products were split so each generic medication may be classified accordingly. Only medications that were used at least once between initiation of ceftaroline therapy (Day 1) and the day of pharmacokinetic sampling were considered. In the event a stop date was not provided, the patient was assumed to have continuously received the medication from start date until end of study. Topically administered medications were excluded from analysis given that systemic exposure to these agents is generally considered to be negligible.

Statistical Methods: For concomitant medication categories with ≥5 patients using at least one medication in a specified category, a non-parametric Wilcoxon Rank-Sum text was performed to determine if there was a statistically significant difference in ceftaroline exposure relative to all other patients who did not use at least one medication in the specified category. For each concomitant medication category determined to significantly impact ceftaroline exposure, summary statistics of patient characteristics with a statistically significant impact on ceftaroline pharmacokinetics (e.g., age, gender, CrCL) were calculated separately for those who had at least one drug in the specified category and those that did not.

Population predicted ceftaroline exposures (i.e., C_{max} and AUC_{0-12}) were adjusted for age, gender, and CrCL, since these statistically significant covariates were included in the final population pharmacokinetic model for ceftaroline. Individual predictions of C_{max} and AUC_{0-12} accounted for inter-individual variability around population predictions, and any impact of concomitant medications was expected to translate into either a decrease or increase of individual C_{max} and AUC_{0-12} relative to population predicted exposures.

RESULTS

Concomitant Medication Use: In total, 220 cSSSI or CAP patients who were administered ceftaroline fosamil and included in the population pharmacokinetic analyses were used for this analysis. A summary of concomitant medication use by specified categories is provided in **Table 2**.

Ceftaroline Exposure by Concomitant Medication: There were four concomitant medication categories that appeared to have statistically significant higher values for ceftaroline AUC_{0-12}, but none with C_{max}. Regarding CYP450 drugs, patients using CYP1A2 inhibitors (p=0.018) or CYP3A4/5/7 inhibitors (p=0.005) had statistically significant higher AUC_{0-12} by 19.0% and 20.3%, respectively, than patients not using a drug in these concomitant medication categories (**Figure 1**). It should be noted that several patients were concurrently using either ciprofloxacin (n=5) and amiodarone (n=4), which were the predominant medications in both CYP1A2 and CYP3A4/5/7 inhibitor categories.

Regarding renal drugs, patients using anionic drugs known to undergo active tubular secretion in the kidneys or known vasodilators also had statistically significant higher AUC_{0-12} ($p \leq 0.001$) by 17.6% and 16.6%, respectively, than patients not using a drug in these categories (**Figure 2**). The Sponsor theorizes it is possible that other anionic medications may compete with ceftaroline (an anionic drug) for active transport in the renal proximal tubule, which may have caused greater ceftaroline exposures. Contrastingly, higher AUC_{0-12} values were not anticipated for patients using known vasodilators as these drugs were expected to increase renal clearance and subsequently result in lower, not higher, ceftaroline exposures.

Table 2. Number of Phase 2/3 patients by concomitant medication category

Drug Category	Substrates		Inhibitors		Inducers	
CYP1A2	Acetaminophen	(n=76)	Ciprofloxacin	(n=5)	Insulin	(n=23)
	Theophylline	(n=10)	Amiodarone	(n=4)	Omeprazole	(n=10)
	Ondansetron	(n=7)	Levofloxacin	(n=4)		
	Verapamil	(n=4)				
	Estradiol	(n=3)				
	Warfarin	(n=3)				
	Amitriptyline	(n=2)				
	Tizanidine	(n=2)				
	Cyclobenzaprine	(n=1)				
	Haloperidol	(n=1)				
	Mexiletine	(n=1)				
	Naproxen	(n=1)				
	Propanolol	(n=1)				
CYP2B6	Methadone	(n=13)	–		–	
	Efavirenz	(n=1)				
CYP2C8	–		Montelukast	(n=2)	–	
			Gemfibrozil	(n=1)		
CYP2C9	Diclofenac	(n=30)	Amiodarone	(n=4)	–	
	Ibuprofen	(n=26)	Fluconazole	(n=2)		
	Glibenclamide	(n=5)	Sertraline	(n=2)		
	Glimepiride	(n=4)	Fluvastatin	(n=1)		
	Glipizide	(n=3)	Isoniazid	(n=1)		
	Warfarin	(n=3)	Lovastatin	(n=1)		
	Amitriptyline	(n=2)				
	Fluoxetine	(n=1)				
	Fluvastatin	(n=1)				
	Lornoxicam	(n=1)				
	Losartan	(n=1)				
	Naproxen	(n=1)				
	Piroxicam	(n=1)				
	Rosiglitazone	(n=1)				
CYP2C19	Omeprazole	(n=10)	Omeprazole	(n=10)	Prednisone	(n=5)
	Pantoprazole	(n=10)	Pantoprazole	(n=10)		
	Diazepam	(n=7)	Paroxetine	(n=5)		
	Warfarin	(n=3)	Fluoxetine	(n=1)		
	Amitriptyline	(n=2)	Lansoprazole	(n=1)		
	Carisoprodol	(n=1)	Topiramate	(n=1)		
	Citalopram	(n=1)				
	Lansoprazole	(n=1)				
	Propanolol	(n=1)				
CYP2D6	Lidocaine	(n=23)	Diphenhydramine	(n=30)	Dexamethasone	(n=7)
	Metoprolol	(n=14)	Methadone	(n=13)		
	Codeine	(n=9)	Ranitidine	(n=11)		
	Tramadol	(n=8)	Metoclopramide	(n=7)		
	Metoclopramide	(n=7)	Paroxetine	(n=5)		
	Ondansetron	(n=7)	Amiodarone	(n=4)		
	Oxycodone	(n=7)	Escitalopram	(n=4)		
	Promethazine	(n=6)	Hydroxyzine	(n=2)		
	Carvedilol	(n=5)	Citalopram	(n=1)		
	Paroxetine	(n=5)	Fluoxetine	(n=1)		
	Amitriptyline	(n=2)				
	Venlafaxine	(n=2)				
	Aripiprazole	(n=1)				
	Dextromethorphan	(n=1)				
	Fluoxetine	(n=1)				
	Haloperidol	(n=1)				
	Mexiletine	(n=1)				
	Nebivolol	(n=1)				
	Propanolol	(n=1)				
	Timolol	(n=1)				

CYP2E1	Halothane Isoflurane Sevoflurane	(n=3) (n=2) (n=1)	–		Isoniazid	(n=1)
CYP3A4/5/7	Lidocaine Fentanyl Midazolam Methadone Atorvastatin Codeine Amlodipine Dexamethasone Diazepam Ondansetron Salmeterol Alprazolam Simvastatin Verapamil Clarithromycin Estradiol Hydrocortisone Nifedipine Diltiazem Domperidone Finasteride Quetiapine Alfentanil Aripiprazole Cilostazol Dextromethrophan Felodipine Haloperidol Lovastatin Propanolol	(n=23) (n=20) (n=15) (n=13) (n=9) (n=9) (n=8) (n=7) (n=7) (n=7) (n=7) (n=6) (n=6) (n=4) (n=3) (n=3) (n=3) (n=3) (n=2) (n=2) (n=2) (n=2) (n=1) (n=1) (n=1) (n=1) (n=1) (n=1) (n=1) (n=1)	Ciprofloxacin Amiodarone Verapamil Clarithromycin Diltiazem Fluconazole Itraconazole	(n=5) (n=4) (n=4) (n=3) (n=2) (n=2) (n=1)	Efavirenz Pioglitazone	(n=1) (n=1)
Renal anions undergoing active renal secretion	Cefotaxime Metronidazole Penicillin Ceftazidime	(n=14) (n=7) (n=3) (n=2)	Hydrochlorothiazide Ciprofloxacin Cefuroxime Folic acid	(n=20) (n=5) (n=2) (n=1)	Amoxicillin Furosemide Ampicillin Cefazolin	(n=27) (n=27) (n=14) (n=6)
Renal cations undergoing active renal secretion	Vancomycin	(n=6)	Morphine Digoxin	(n=24) (n=6)	Ranitidine	(n=11)
Vasodilator drugs & others that increase renal blood flow	Linsopril Carvedilol Ramipril Nitrous oxide	(n=6) (n=5) (n=5) (n=2)	Enalapril Isosorbide Perindopril Mannitol Nicardipine	(n=41) (n=8) (n=5) (n=1) (n=1)	Captopril Nifedipine Fosinopril Quinapril	(n=4) (n=3) (n=2) (n=1)
Vasoconstrictor drugs & others that decrease renal blood flow	Norepinephrine	(n=1)	Desmopressin	(n=1)	Epinephrine	(n=2)

Figure 1. Change in ceftaroline AUC_{0-12} for concomitant **CYP1A2 inhibitors (top)** and **CYP3A4/5/7 inhibitors (bottom)**

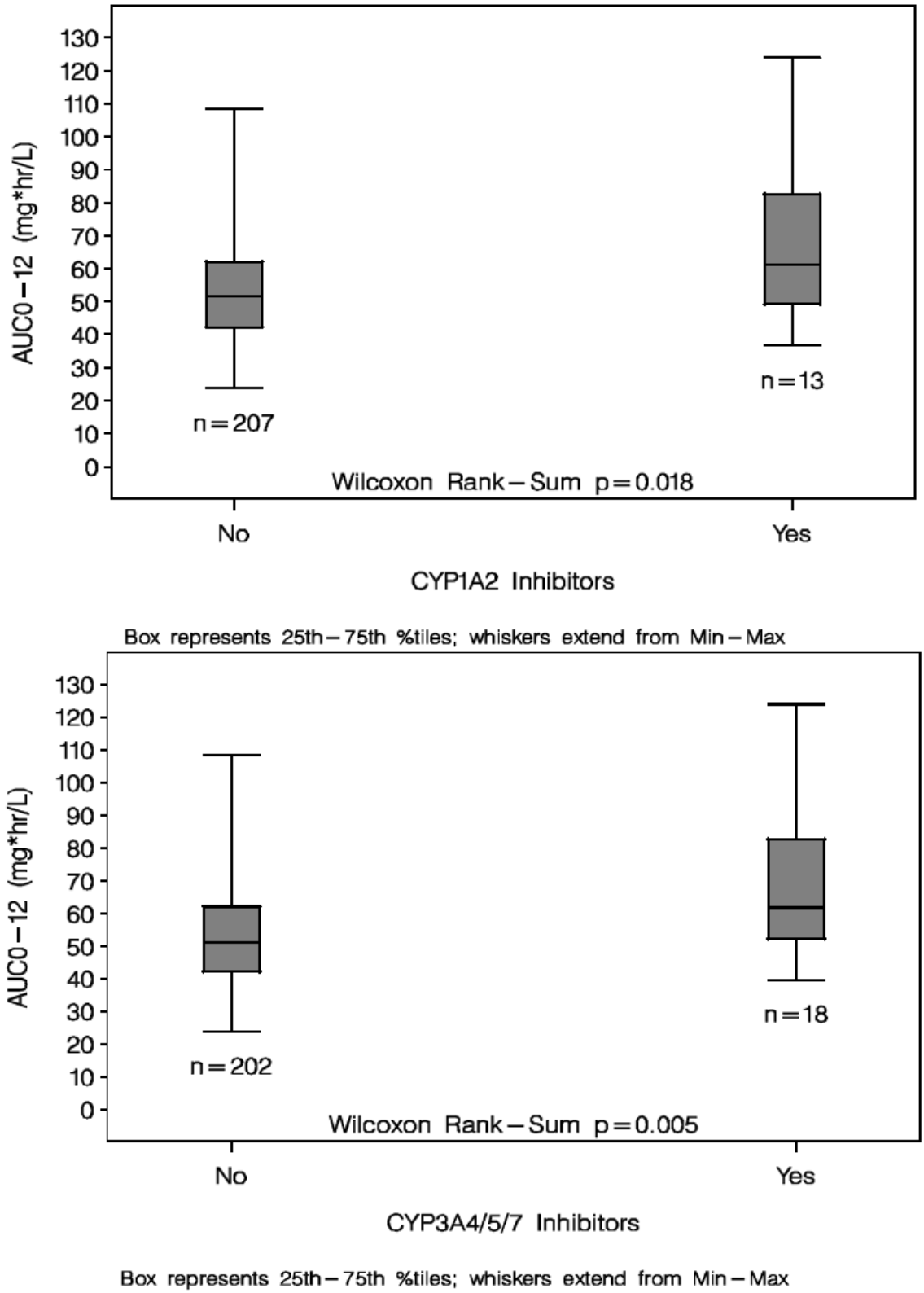
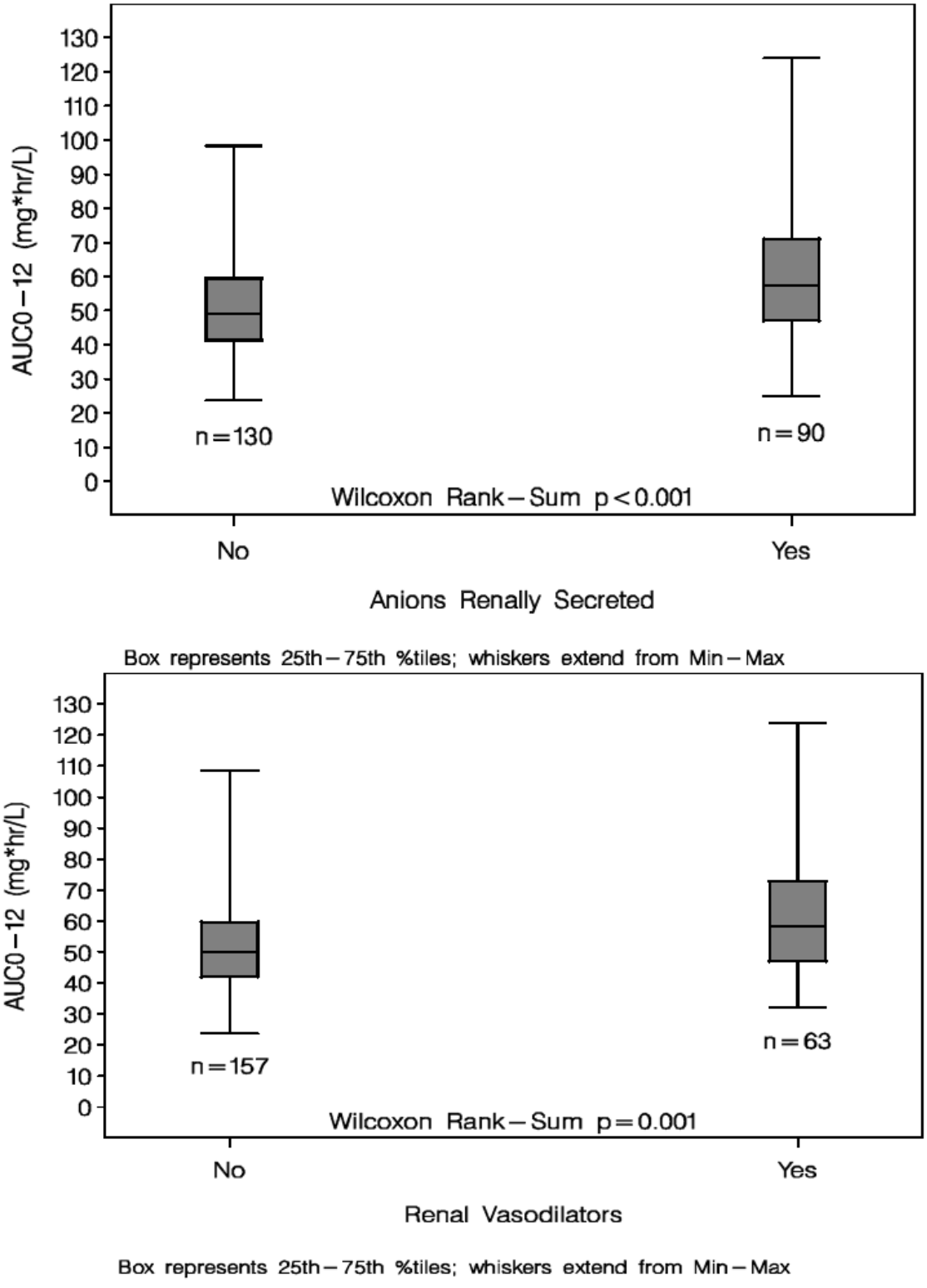


Figure 2. Change in ceftaroline AUC_{0-12} for concomitant **anions undergoing active renal secretion (top)** and **vasodilator drugs that increase renal blood flow (bottom)**



The Sponsor notes the exploratory nature of these findings and indicates the effect of confounding factors. Potential confounders included age and renal function, as patients having used at least one drug in each of the four concomitant medication categories were generally older and had lower CrCL than those who did not use a drug in the specified categories (**Table 3**).

Table 3. Patient characteristics of those not having used versus those having used at least one drug in the statistically significant concomitant medication categories

Concomitant medication / Patient characteristic	Patients NOT using a drug in the specified category	Patients using a drug in the specified category
CYP1A2 inhibitors		
N	207	13
% Male	58.5%	53.9%
Median Age (yr)	52.0	71.0
Median CrCL (mL/min/1.73m^2)	92.1	58.3
CYP3A4/5/7 inhibitors		
N	202	18
% Male	57.4%	66.7%
Median Age (yr)	52.0	67.0
Median CrCL (mL/min/1.73m^2)	92.1	58.2
Renal anions undergoing active renal secretion		
N	130	90
% Male	58.5%	57.8%
Median Age (yr)	49.0	61.5
Median CrCL (mL/min/1.73m^2)	97.2	71.7
Vasodilator drugs & others that increase renal blood flow		
N	157	63
% Male	61.2%	50.8%
Median Age (yr)	48.0	67.0
Median CrCL (mL/min/1.73m^2)	101	61.9

Moreover, differences in ceftaroline AUC_{0-12} by concomitant medication use could be partly attributed to demographics and renal function when comparing AUC_{0-12} estimates by individual versus population predictions, which adjust for gender, age, and CrCL covariates (**Table 4**). For vasodilator drugs, nearly all of the 16.6% difference in ceftaroline AUC_{0-12} from individual predictions could be attributed to differences in patient characteristics, as a 16.2% difference was estimated with population predictions. For renal anions, CYP1A2 inhibitors, and CYP3A4/5/7 inhibitors, AUC_{0-12} differences of 4.23%, 6.46%, and 9.17%, respectively, could be attributed to demographics and renal function based on population predictions. Remaining differences of 13.4%, 12.5%, and 11.1%, respectively, could be attributed to other unknown factors, which may include concomitant medication use.

Table 4. Individual versus population predicted ceftaroline AUC_{0-12} for patients not having used and patients having used at least one drug in the statistically significant concomitant medication categories

Concomitant medication / Predicted AUC_{0-12}	Median ceftaroline AUC_{0-12} (mg*L/h)		Magnitude of higher median AUC_{0-12}
	Patients NOT using a drug in the specified category	Patients using a drug in the specified category	
CYP1A2 inhibitors			
Population	48.0	51.1	6.46%
Individual	51.5	61.3	19.0%
CYP3A4/5/7 inhibitors			
Population	48.0	52.4	9.17%
Individual	51.3	61.7	20.3%
Renal anions undergoing active renal secretion			
Population	47.3	49.3	4.23%
Individual	48.9	57.5	17.6%
Vasodilator drugs & others that increase renal blood flow			
Population	46.3	53.8	16.2%
Individual	49.9	58.2	16.6%

SPONSOR'S CONCLUSIONS: Following *post-hoc* analysis of ceftaroline exposures (C_{max} and AUC_{0-12}) in Phase 2/3 patients with cSSSI or CAP receiving concomitant medications by using population pharmacokinetic models:

- None of the concomitant medication categories produced a statistically significant difference in ceftaroline C_{max}.
- Concomitant use of CYP1A2 inhibitors (p=0.018) or CYP3A4/5/7 inhibitors (p=0.005) resulted in statistically significantly higher AUC_{0-12} values than patients not using a drug in these categories. The magnitude of the difference in median AUC_{0-12} for both drug classes, before accounting for differences in patient characteristics, was approximately 20% and should not warrant dose adjustment.
- Concomitant use of anionic drugs known to under active tubular secretion in the kidneys or medications with vasodilatory effects resulted in statistically significantly higher AUC_{0-12} values ($p \leq 0.001$) than patients not using a drug in these categories. The magnitude of the difference in median AUC_{0-12} for both drug classes, before accounting for differences in patient characteristics, was approximately 16-18% and should not warrant dose adjustment.
- In each concomitant medication class that produced a statistically significant higher AUC_{0-12}, patients using these agents were older and had worse renal function than those not using a drug in these classes.
- After adjusting for differences in demographics and renal function, the difference in AUC_{0-12} for patients taking vasodilators appeared to be fully explained by patient characteristics, while 12.5%, 11.1%, and 13.4%, respectively, for patients taking CYP1A2 inhibitors, CYP3A4/5/7 inhibitors, and anionic drugs appeared to be attributed to other factors. These remaining unexplained differences in AUC_{0-12} for the three concomitant medication classes were not considered clinically meaningful.
- This analysis should be considered exploratory in nature and not confirmatory since drug-drug interactions are typically conducted in a well-controlled Phase 1 study setting using a model drug for each concomitant medication category.

REVIEWER ASSESSMENT: The Sponsor's conclusions are appropriate based on study results.

4.2 Pharmacometrics Review

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the Exposure-Response Relationship Support the Evidence of Effectiveness at the Proposed Dose?

For the complicated skin and skin-structure infections (cSSSI), the exposure-response relationship supports the proposed dose (600mg q12h). The estimated free drug %T>MIC was greater than 38% (higher than the PK/PD target of 20-30% associated with bacteriostasis effect against *S. aureus* known for cephalosporins) in all the microbiologically evaluable (ME) patients infected by *S. aureus* or *S. pyogenes* or both (**Figure 1**). Logistic regression analysis of the free-drug %T>MIC versus the per-patient microbiological response in cSSSI patients showed a significant positive relationship (p=0.027). The probability of per-patient microbiological response is greater than 80% and increases with increasing %T>MIC as shown in **Figure 2**.

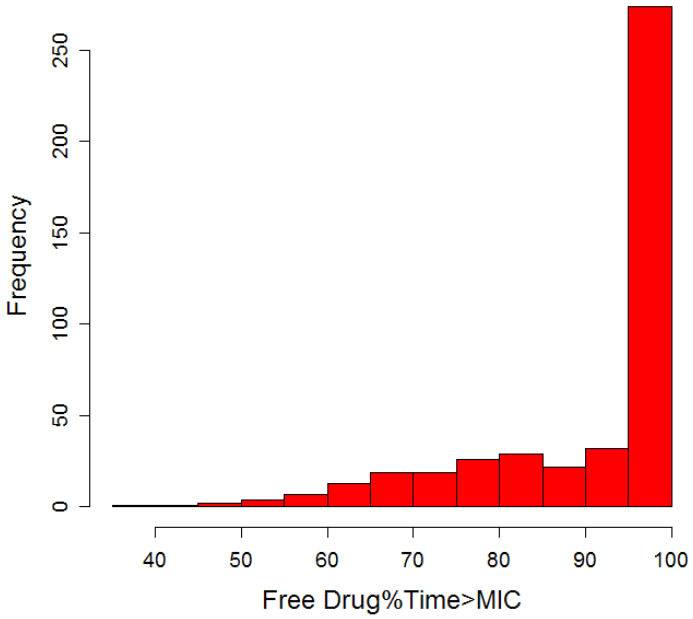


Figure 1: Distribution of the free drug %T>MIC values in the ME population infected by *S. aureus* or *S. pyogenes* or both, n =449

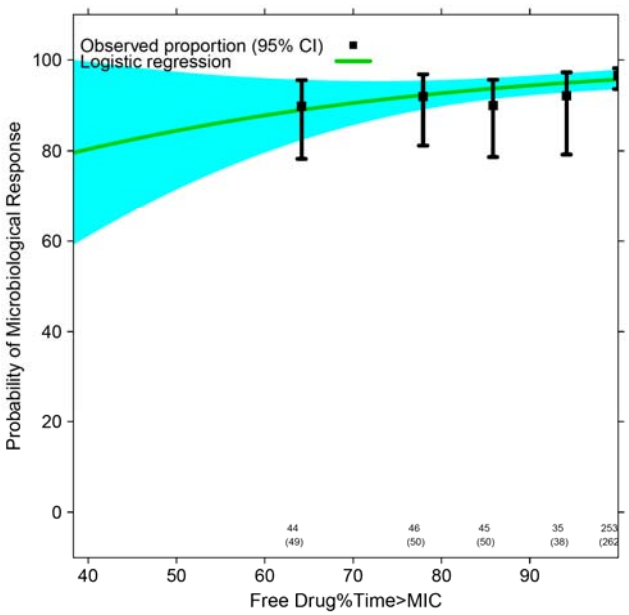


Figure 2: Univariate relationship between the proportion of patients with favorable microbiological response and free drug %T>MIC for the ME population infected by *S. aureus* or *S. pyogenes* or both, n =449. *The solid line represents the mean logistic regression prediction. The black symbols represent the observed percentage of patients who had favorable microbiological response in each %T>MIC bin. The shaded area represents the 95% confidence interval of the prediction*

Note: ME population included patients from Phase 2 studies P903-03 & P903-19 (IM dosing), and Phase 3 studies P903-06 & -07. The individual estimate for patients with PK (n=41 from IV dosing, n=42 from IM dosing) and population mean predicted concentration for patients without PK were used to derive free ceftaroline %T>MIC for each evaluable patient

For the community-acquired bacterial pneumonia (CABP), the exposure-response relationship was not identified due to target attainment in the majority of patients. Over 90% patients in the ME population had free-drug %T>MIC greater than 90%, therefore, the free-drug %T>MIC range was not broad enough to inform an exposure-efficacy relationship. However, the target attainment (i.e. %T>MIC greater than 40%, which is the PK/PD target associated with bacteriostasis against *S. pneumoniae* known for cephalosporins) achieved in all the patients infected by *S. pneumoniae* supports the proposed dose (600 mg q12h) for CABP.

1.1.2 Are there any predictors of low microbiological response to ceftaroline in addition to the free drug %T>MIC?

Age and diabetes status, in addition to the free drug %T>MIC, were identified as the potential predictors of low response to ceftaroline in cSSSI patients (**Table 1**). Older patients (Age > 60 years of age) or patients with diabetes likely have a lower response rate than younger patients (Age ≤ 60 years of age) or non-diabetic patients, respectively. Other factors including body weight and BMI were evaluated but found not to be significant predictors of low response.

Table 1: Proportion test for factors associated with per-patient microbiological response for the ME population infected by *S. aureus* or *S. pyogenes* or both, n=449

	Independent variable	Per-patient microbiological response rate		CI 95%	Chi-square p-value
		YES	NO		
CSSSI ME population with *S aureus* or *S. pyogenes* (n= 449)	Age > 60 years	0.88 (n=78)	0.95 (n=371)	(-0.15, 0.01)	0.03
	Diabetes	0.86 (n=72)	0.96 (n=377)	(-0.187, -0.005)	0.003

Only 41 patients out of the ME population (n=449) had PK sample taken and with the estimated steady-state AUCτ based on the pop PK model. In this subset of patients, three and seven patients are older than 60 years and diabetic, respectively. Similar to the ME population, patients older than 60 years of age (2/3) or diabetic patients (5/7) in this subset had a lower response rate than younger patients (36/38) or non-diabetic patients (33/34), respectively. As shown in **Figure 3**, the patients > 60 years of age had a significantly higher mean steady-state AUCτ than the patients ≤ 60 years of age. In **Figure 4**, the AUCτ mean values are similar and independent of diabetes status. Because this subset of patients is limited in number (<10% of the ME population) and not necessarily fully represent the ME population, the reviewer speculates that that the low response in patients > 60 years of age or patients with diabetes may be not due to the difference on ceftaroline plasma exposure in the respective subgroups. In fact, ceftaroline plasma levels are higher in older patients compared to younger patients.

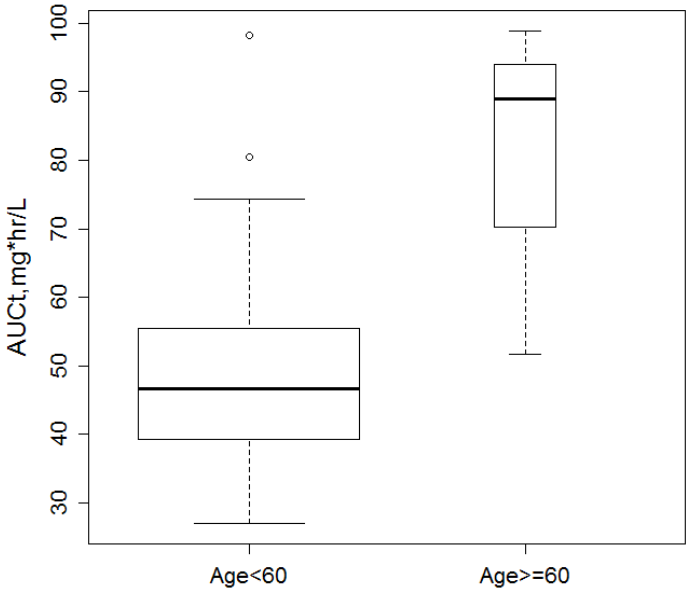


Figure 3: Comparison of ceftaroline plasma AUCτ in two age groups (≤ 60 years of age, n=38 *vs*. >60 years of age, n=3) in the ME population with the estimated exposure data. *AUCτ was estimated as the AUC for the 12-hour dosing interval at the steady state; 2 out 3 elderly patients vs. 36 out of 38 younger patients had favorable microbiological response*

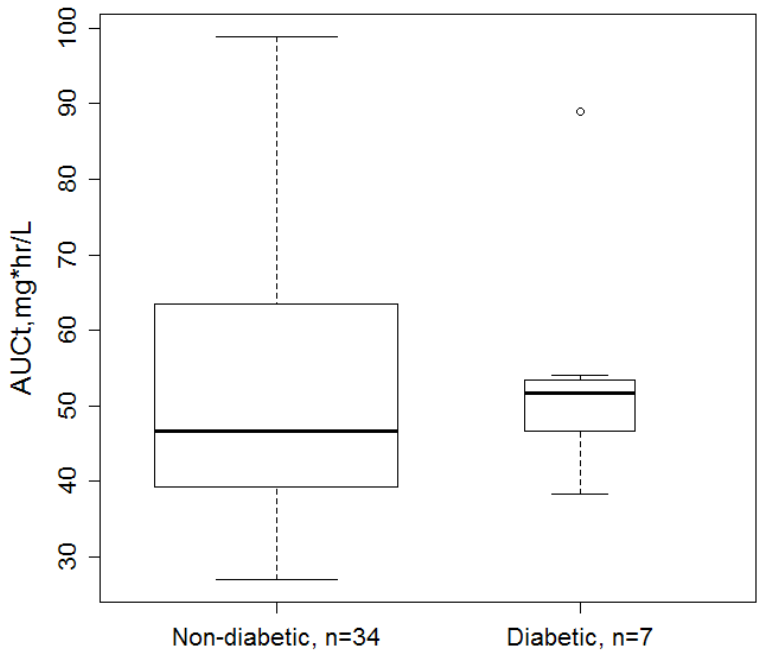


Figure 4: Comparison of ceftaroline plasma AUCτ (mean ± SD) based on diabetes status: with diabetes (54.1 ± 16.4 mg•hr/L) *vs.* without diabetes (50.8 ± 18.2 mg•hr/L) in the cSSSI PK patients who also had the record on diabetes status. *Five out 7 diabetic patients vs. 33 out of 34 non-diabetic patients had favorable microbiological response*.

1.1.3 Does the ceftaroline exposure data support the proposed dose adjustment based on renal function (i.e. creatinine clearance, CrCL in mL/min)?

The sponsor proposed (b) (4) for patients with moderate and severe renal impairment (CrCL >10-50 mL/min) and (b) (4) for patients with mild (CrCL >50-80 mL/min) renal impairment.

All patients in the cSSSI PK population (n=92) had CrCL >50 mL/min and were administered with the 600 mg q12h dose. All patients in the CAP PK population (n=127) had CrCL >30 mL/min and were administered with either 600 mg q12h dose (CrCL >50 mL/min) or 400 mg q12h dose (CrCL>30-50 mL/min).

As shown in **Figure 5** (upper graph), the observed ceftaroline plasma concentrations following a single 600 mg dose in patients with moderate renal impairment tend to be higher than those in patients with normal or mild renal impairment receiving the same 600 mg dose. When the dose was adjust to 400 mg (lower graph) for CABP patients with moderate renal impairment in the clinical trial, the observed ceftaroline plasma concentration-time profiles overlap with those in CABP patients of normal renal function (600 mg q12h) or mild renal impairment (600 mg q12h). Furthermore, the boxplot (**Figure 6**) showed that ceftaroline exposure measured by AUCτ in patients with moderate renal impairment (400mg q12h) were comparable to that in patients with

mild renal impairment (600mg q12h) and approximately 37% higher than that in patients with normal renal function. These data support the need for dose adjustment based on renal function (i.e. CrCL) and confirmed that the dose adjustment (b) (4) proposed for patients with moderate renal is appropriate.

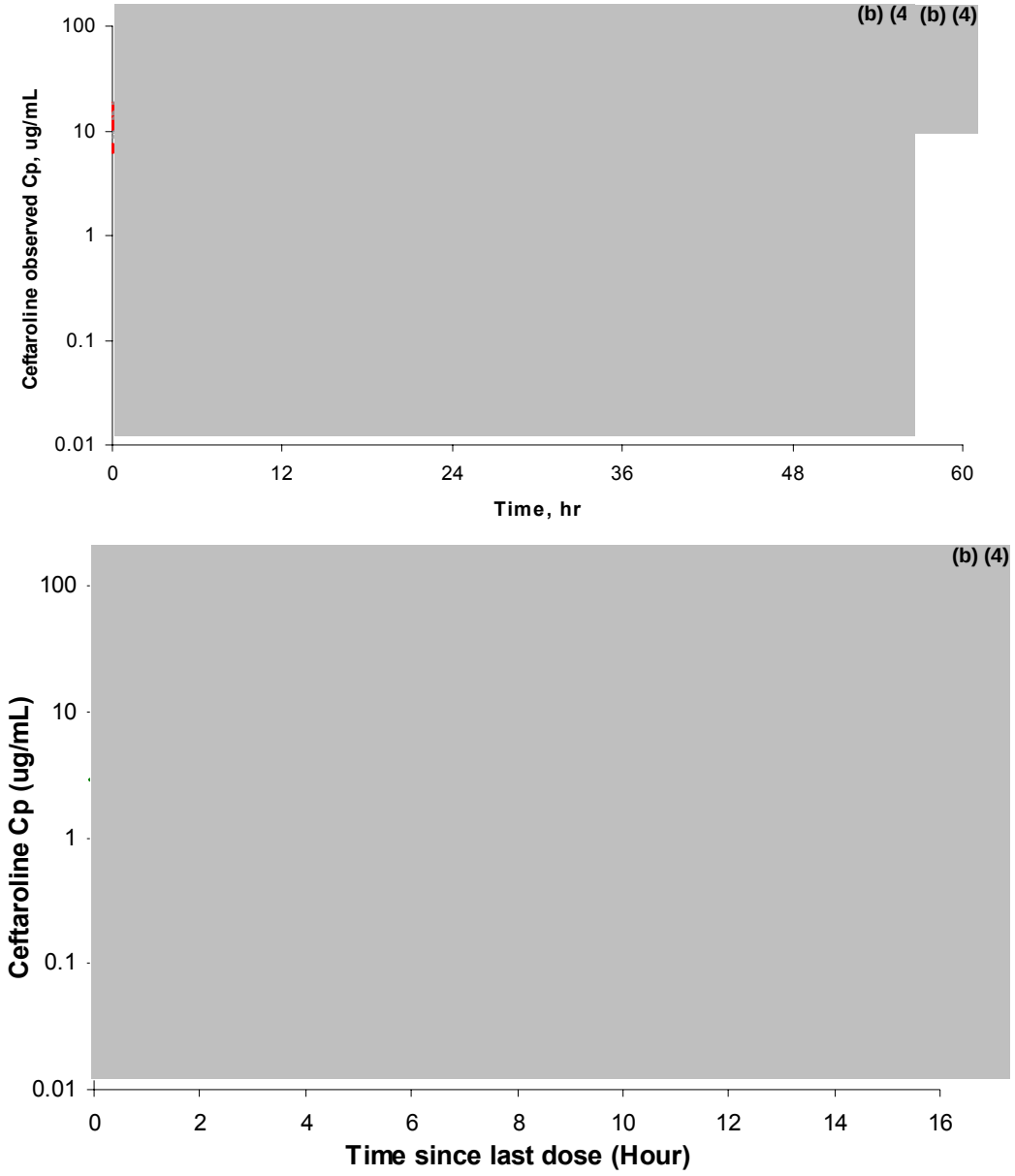


Figure 5: The observed ceftaroline plasma concentrations-time profiles in the Phase 1 study P903-02 (Upper graph) and CABP PK patients (Lower graph) with moderate or mild renal impairment, or normal renal function

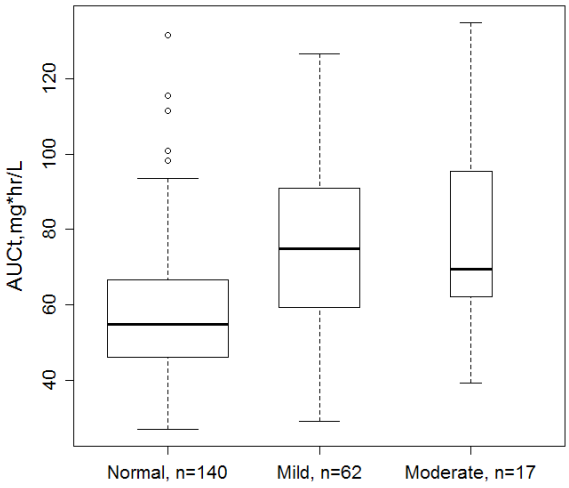


Figure 6: Ceftaroline AUCτ (mean ± SD) in the combined CSSSI PK and CABP PK population with moderate renal impairment (400 mg q12h; 79.2 ± 26.0 mg•hr/L), mild renal impairment (600 mg q12h; 77.8 ± 21.6 mg•hr/L), and normal renal function (600 mg q12h; 64.9 ± 18.4 mg•hr/L). *The cSSSI PK population includes 92 patients in Phase 2 study P903-03 and Phase 3 studies P903-06 & 903-07. The CABP PK population includes 127 patients in Phase 3 Studies P903-08 and P903-09*

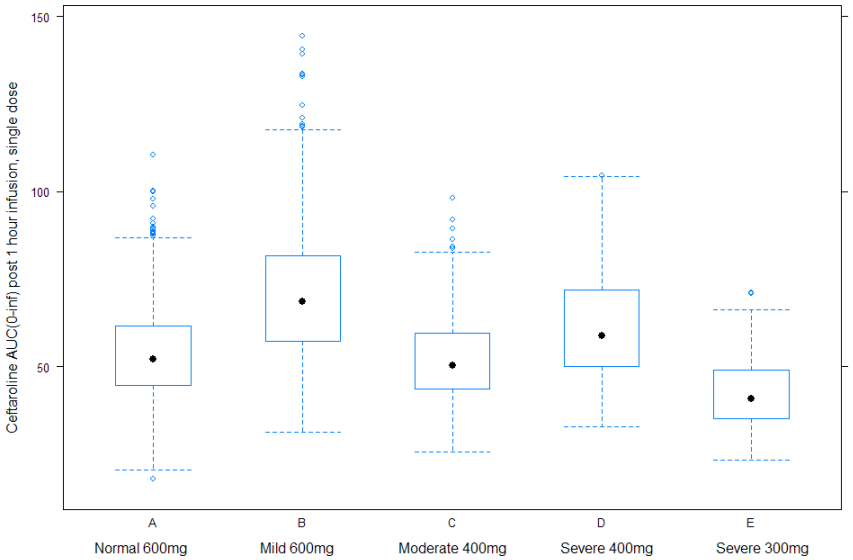


Figure 7: Predicted ceftaroline AUC $_{0\text{-inf}}$ for a simulated patient population (n=2000) constructed based on demographic characteristics of the CABP PK subjects and Phase 1 subjects with severe renal impairment. Single dose of 600 mg, 400 mg or 300 mg administered to patients with normal renal function or different level of renal impairment. *Mean AUCτ in mg•hr/hr= 53.6 (normal), 70.6(mild), 52.0 (moderate), 60.9(Severe -400 mg) and 42.8 (Severe -300 mg)*

Only a limited number of cSSSI and CABP patients with severe renal impairment (CrCL> 10-30 mL/min) were enrolled in the clinical trials and there was no PK data obtained from these patients. Using a simulation approach (**Figure 7**), the reviewer explored two different dosing regimens for patients with severe renal impairment. The simulation results showed that 400 mg q12h dosing regimen for patients with severe renal impairment would yield ceftaroline exposure comparable to that in patients with normal renal function receiving 600 mg q12h dose. The model has several limitations (see reviewer's comments) and the implications on model predictions are not obvious. Please see Clinical Pharmacology review for derivation of dosing recommendations based on Phase I renal impairment studies. As shown in **Figure 8**, PK results for the Phase 1 designated renal impairment studies (P903-02, 04 & 18) clearly showed that ceftaroline plasma clearance is inversely related to the severity of the renal impairment (Ph1_A, B, C or D), and this downward trend is in parallel with what was observed in patient population (Ph2&3_A, _B or _C).

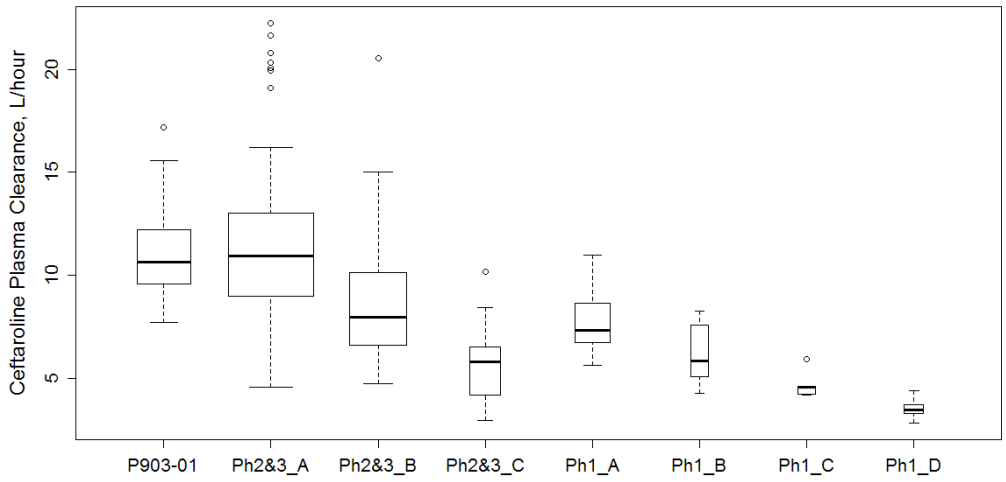


Figure 8: Ceftaroline plasma clearance estimated by the population PK model across different studies. P903-01 represent healthy subjects (n=54) from Phase 1 Study P903-01. Ph2&3_A, Ph2&3_B and Ph2&3_C represent Phase 2/3 patients with normal renal function (n=140, 600 mg q12h), mild renal function (n=62, 600 mg q12h), and moderate renal function (n=17, 400mg q12h), respectively. Ph1_A, Ph1_B, Ph1_C and Ph1_D represent subjects from the Phase 1 renal impairment PK Studies P903_02/04/18 with normal renal function (n=23, 600 or 400 mg single dose), mild renal impairment (n=6, 600 mg single dose), moderate renal impairment (n=6, 600 mg single dose), and severe renal impairment (n=6, 400 mg single dose), respectively

1.2 Recommendations

The reviewer concurs with the dose proposed (600 mg q12h) by the sponsor and that the dose should be adjusted based on the renal function (i.e., the estimated or measured creatinine clearance.

1.3 Label Statements

(b) (4)

2 PERTINENT REGULATORY BACKGROUND

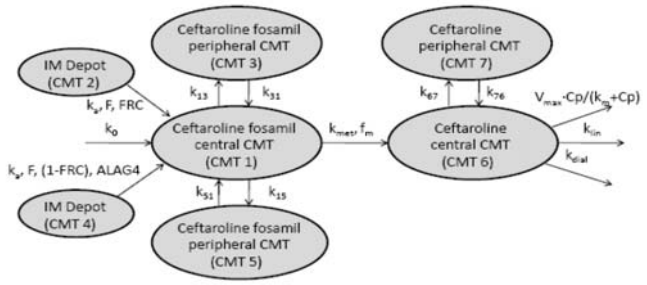
Ceftaroline fosamil is the prodrug of ceftaroline, which is a cephalosporin antibiotic with broad spectrum activity against both gram-positive and gram-negative organisms. The sponsor conducted two (four total) randomized, multinational, active-controlled, double-blind Phase 3 trials in adult patients to support each indication: the treatment of complicated skin and skin structure infections (cSSSI) and community-acquired bacterial pneumonia (CABP).

The sponsor proposed that the recommended dosing regimen for ceftaroline fosamil is 600 mg administered as a 1-hour intravenous (IV) infusion every 12 hours (q12h) for 5 to 14 days for cSSSI and 5 to 7 days for CABP. Patients with renal insufficiency should have the dosage adjustment based on the estimated or measured creatinine clearance (CrCL).

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK analysis

The sponsor developed a population pharmacokinetic model (**Figure 9** and **Table 2**) to characterize the plasma concentration-time data for the prodrug and active ceftaroline and the impact of various subject covariates on PK of ceftaroline following IV and IM dosing of ceftaroline fosamil to Phase 1 healthy subjects (n=185) and Phase 2/3 cSSSI patients (n=92). The population PK analysis was conducted using the FOCE method with η-ε interaction in NONMEM® VI.



Where:

k_0 = Fixed zero-order IV infusion rate of the prodrug (mg/hr)
k_{met} = First-order conversion rate constant of the prodrug to active ceftaroline (hr^{-1}); $k_{met} = CL_p/Vc_p$
f_m = Fraction of the prodrug converted to active ceftaroline (not estimated)
k_{13} = First-order transfer rate constant of prodrug from the central to first peripheral CMT (hr^{-1}); $k_{13} = CLd1_p/Vc_p$
k_{15} = First-order transfer rate constant from the prodrug central to second peripheral CMT (hr^{-1}); $k_{15} = CLd2_p/Vc_p$
k_{31} = First-order transfer rate constant from the first prodrug peripheral to central CMT (hr^{-1}); $k_{31} = CLd1_p/Vp1_p$
k_{51} = First-order transfer rate constant from the second prodrug peripheral to central CMT (hr^{-1}); $k_{51} = CLd2_p/Vp2_p$
CL_p= Total plasma clearance for the prodrug (L/hr)
Vc_p = Central volume of distribution for the prodrug (L)
$Vp1_p$ = Volume of distribution for the first prodrug peripheral CMT (L)
$Vp2_p$ = Volume of distribution for the second prodrug peripheral CMT (L)
$CLd1_p$ = Distribution clearance between the prodrug central and first peripheral CMT (L/hr)
$CLd2_p$ = Distribution clearance between the prodrug central and second peripheral CMT (L/hr)
Vss_p = Steady-state volume of distribution for the prodrug (L); $Vss_p = Vc_p + Vp1_p + Vp2_p$
k_a = First-order rate constant for prodrug appearance in plasma after IM dosing (hr^{-1})
F = Estimated IM bioavailability fraction for the prodrug
FRC = Fraction of the prodrug dose that initially appears in plasma after IM dosing
ALAG4 = Delay in appearance of a fraction of the prodrug dose in plasma after IM dosing (hr)
V_{max}= Maximum elimination rate for the saturable elimination pathway (mg/hr)
k_m= Michaelis-Menton constant; ceftaroline concentration producing an elimination rate that is 50% of V_{max} (mg/L)
k_{lin} = Parallel first-order elimination rate constant for ceftaroline (hr^{-1})
k_{dial} = First-order elimination rate constant for ceftaroline during dialysis (hr^{-1})
k_{67} = First-order transfer rate constant of ceftaroline from the central to peripheral CMT (hr^{-1}); $k_{67} = CLd/Vc$
k_{76} = First-order transfer rate constant of ceftaroline from the peripheral to central CMT (hr^{-1}); $k_{76} = CLd/Vp$
Vc = Central volume of distribution for ceftaroline (L)
Vp = Volume of distribution for the ceftaroline peripheral CMT (L)
Cp = Plasma ceftaroline concentration (mg/L)
CLd = Distribution clearance between the ceftaroline central and peripheral CMT (L/hr)
CL_i = Intrinsic clearance component of ceftaroline clearance (L/hr); $CL_i = V_{max}/k_m$
CL_{lin} = Linear clearance component of ceftaroline clearance (L/hr); $CL_{lin} = Vc \cdot k_{lin}$
CL_{dial} = Dialysis clearance for ceftaroline (L/hr); $CL_{dial} = Vc \cdot k_{dial}$
CL_T = Total plasma clearance of ceftaroline (L/hr); $CL_T = CL_{lin} + CL_i \cdot k_m/(Cp+k_m) + CL_{dial}$
Vss = Steady-state volume of distribution for ceftaroline (L); Vss = Vc + Vp

Figure 9: Final population PK model for ceftaroline fosamil (three-compartment) and active ceftaroline (two-compartment). *Source: ICPD 00173-3*

The covariate assessment identified creatinine clearance (CrCL), age and gender as statistically significant predictors of PK parameters (**Table 2**). The robustness of the final model was assesses using a non-parametric bootstrap method. Furthermore, the Phase 3 PK data from CABP patients (n=127) were used as a separate external validation dataset to assess the predictive performance of the final population PK models for ceftaroline fosamil and active ceftaroline. Finally, the population PK model was utilized to impute ceftaroline exposure at steady-state (C_{max}, AUC_{0-12}, and %T>MIC) for patients who did not have PK sample. The individual estimate for patients with PK and population mean estimates for patients without PK were used in PK-PD analyses for efficacy in patients with cSSSI and CABP.

Table 2: Population mean parameter estimates and their associated precision (%SEM) for the final population PK model for ceftaroline. *Source: ICPD 00173-3*

Parameter	Final estimate	%SEM
CL_i (L/hr) coefficient[a]	11.6	9.24
CL_i-CrCL power	0.441	10.8
CL_i-Age slope	-0.0883	17.0
Increase in CL_i for Phase 2/3 patients (L/hr)	4.11	17.7
Vc (L)[b]	8.67	4.00
Increase in Vc for Phase 2/3 patients (L)	7.02	15.2
CLd (L/hr)[c]	8.59	6.07
Increase in CLd for males (L/hr)	4.88	17.1
Vp (L)[d]	11.7	5.02
Increase in Vp for males (L)	2.87	16.7
K_m (mg/L)	9.62	26.6
CL_{lin} (L/hr) coefficient[e]	3.06	17.7
CL_{lin}-CrCL power	0.343	17.5
ω^2_{CLi}	0.0911 (30.2% CV)	21.5
Covariance (CL_i, K_m)	-0.0927 (r^2 = 0.196)	55.6
ω^2_{Km}	0.449 (67.0% CV)	28.6
ω^2_{Vc}	0.189 (43.5% CV)	25.2
ω^2_{CLd}	0.101 (31.8% CV)	25.8
Covariance (CLd, Vp)	0.0643 (r^2 = 0.959)	25.5
ω^2_{Vp}	0.0426 (20.6% CV)	26.7
σ^2_{SLP}[f]	0.0392	8.74
σ^2_{INT}	0.00180	53.1

a. The population mean CL_i (L/hr) = $11.6 \cdot (CrCL_j/102)^{0.441} - 0.0883 \cdot (Age_j - 36) + 4.11 \cdot POP_j$, where: $CrCL_j$ and Age_j are the baseline CrCL (mL/min/1.73m^2) and age (yr) in the j^{th} subject, and POP_j is an indicator variable in the j^{th} subject with a value of 1 for Phase 2/3 patients and 0 for Phase 1 subjects

b. The population mean Vc (L) = $8.67 + 7.02 \cdot POP_j$

c. The population mean CLd (L/hr) = $8.59 + 4.88 \cdot MALE_j$ where: $MALE_j$ is an indicator variable in the j^{th} subject with a value of 1 for males and 0 for females

d. The population mean Vp (L) = $11.7 + 2.87 \cdot MALE_j$

e. The population mean CL_{lin} (L/hr) = $3.06 \cdot (CrCL_j/102)^{0.343}$

f. Residual variability expressed as a percent coefficient of variation for various predicted concentrations was 105% at 0.05 µg/mL, 62.2% at 0.1 µg/mL, 24.0% at 1 µg/mL, and < 20.0% for concentrations > 25 µg/mL

Reviewer's comment*: The sponsor's population PK model provides a reasonable description of plasma concentration-time profiles for both ceftaroline fosamil and ceftaroline (See* ***Figure 10****). Both age and CrCL, but not body weight, were identified as significant PK covariates, which is consistent to the reviewer's assessment. However, the limitation of the model is that ceftaroline renal clearance, which is the dominant elimination pathway (i.e. >60% excreted in urine as ceftaroline), could not be independently estimated by the model due to the lack of urinary excretion data collected for any of the Phase 2/3 patients. In order to fit the observed data, the total plasma CL was constructed to contain both linear (CL_{linear}) and saturable non-linear elimination (determined by $CL_{Intrinsic}$ and Km) components, both of which were significantly related to creatinine clearance (****Table 2****). As further illustrated in* ***Figure 11*** *and* ***Figure 12****, the non-linear clearance component is concentration-dependent. Therefore, the total plasma clearance is concentration-dependent and changes over time in each dosing interval. The contribution of non-linear component to the total clearance is always higher than that of the linear clearance. It should be note that ceftaroline was shown to have linear pharmacokinetics, as supported by the dose-ranging (50 mg - 1000 mg) Phase 1 PK Study P903-01. Further, the addition of CrCL as a covariate on nonlinear component cannot be supported mechanistically. The reviewer did not reconstruct the sponsor's model by eliminating nonlinear component or*

covariate effect on it due to CrCL. Most of the labeling recommendations made based on the population pharmacokinetic model are verified by using empirical concentration data.

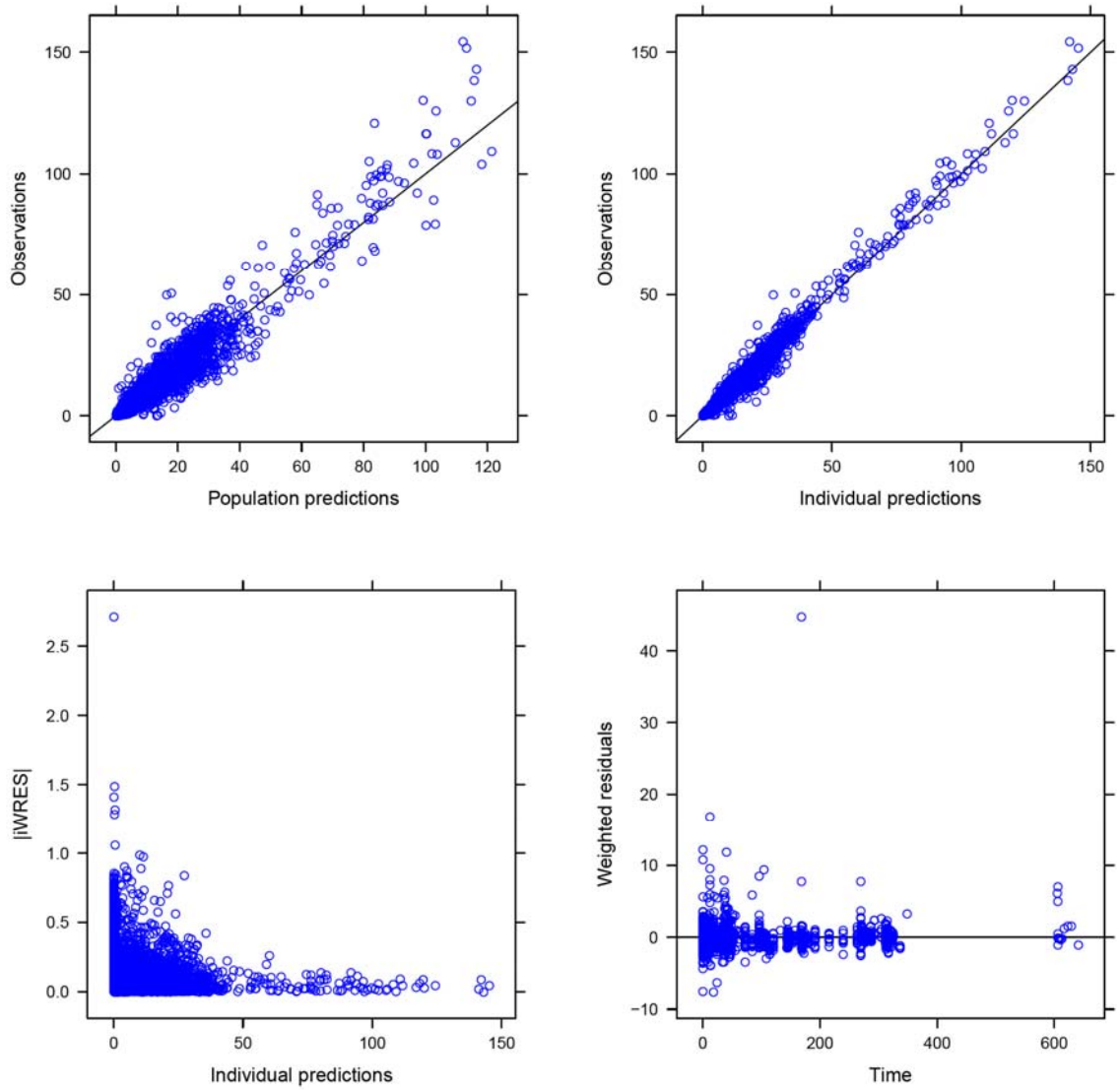


Figure 10: Basic goodness-of-fit plots for the sponsor's final model

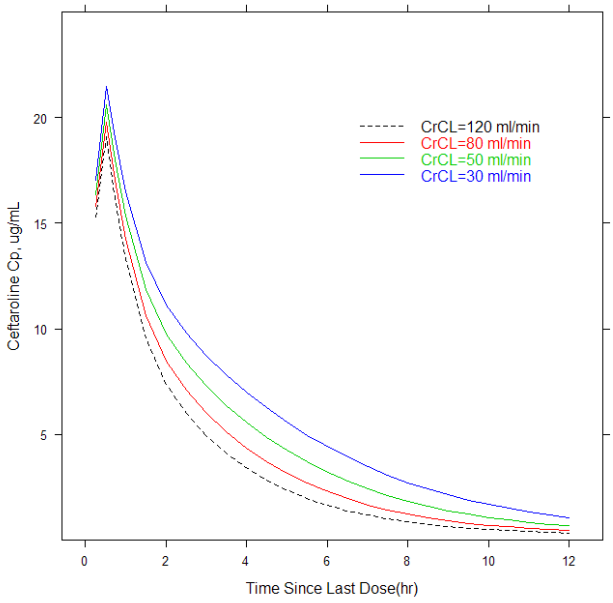


Figure 11: Simulated ceftaroline Cp –time profiles at steady state for four typical subjects of 40 years of age but with different creatinine clearance

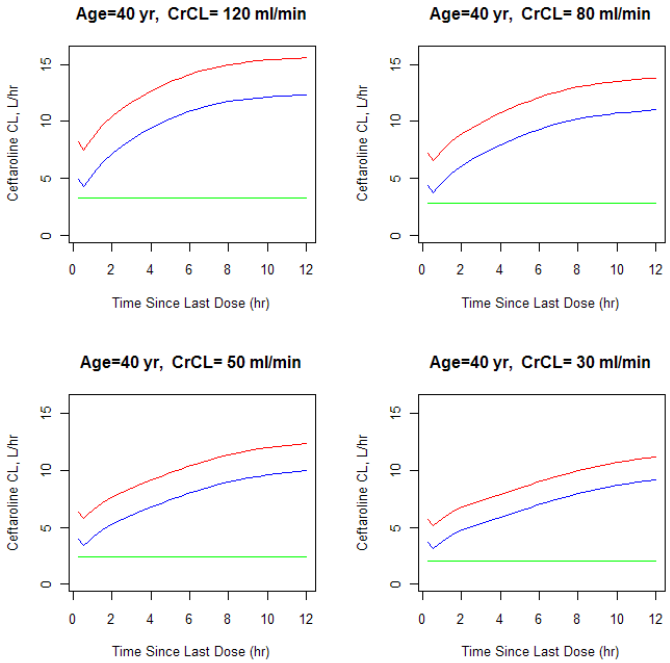


Figure 12: The relationships between total ceftaroline plasma clearance CLt(red line), linear clearance CLl(green line), or saturable non-linear clearance CLnl (blue line), and time illustrated by four typical subjects of 40 years of age but with different creatinine clearance
Note: CLt=CLl+CLnl=CLl+$CL_{intrinsic}$ *Km/(Cp+Km), $CL_{Intrinsic}$ = 11.6 *$(CrCL/102)^{0.441}$, CL_{linear}= 3.06 *$(CrCL/102)^{0.343}$, as described in the sponsor's final pop PK model.

3.2 Exposure-Response Analysis

As PK was not available for all ME patient, Bayesian PK parameter estimates were obtained from the Phase 2 and 3 cSSSI patients based on the final population PK models. The individual estimate for patients with PK and population mean predicted concentration for patients without PK were used to derive the ceftaroline free-drug percent time above MIC (%T>MIC) for each evaluable patient.

For cSSSI, significant univariate logistic relationships between free-drug %T>MIC evaluated as a continuous variable and microbiological response were identified in the entire ME population and among the ME population infected by *S. aureus* (**Figure 13**). Furthermore, multivariable logistic regression analyses were undertaken for these two populations and demonstrated that there are additional patient factors other than free-drug %T>MIC are predictive of per-patient microbiological response. These included age, infection type and presence of bacteremia for all ME patients, and age, infection type, infection location and presence of diabetes for ME patients infected by *S. aureus.*

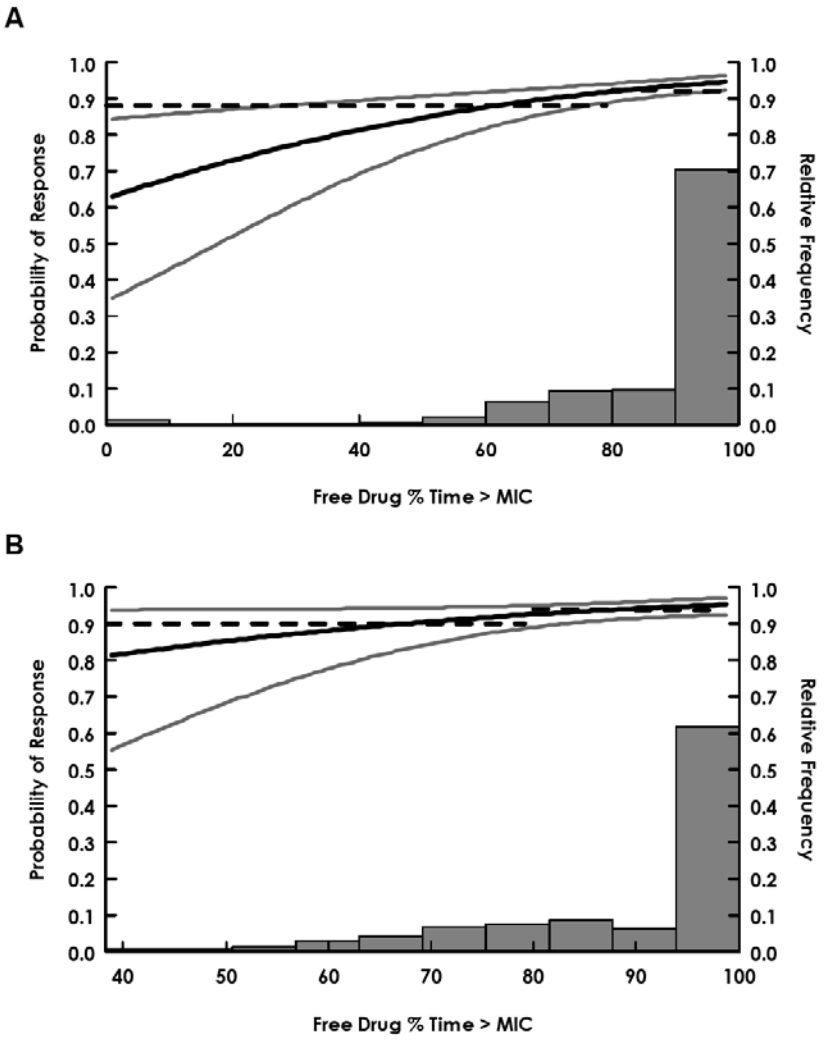


Figure 13: Univariate relationship between the probability of per-patient microbiological response and the free-drug % T > MIC for (A) Total ME population (N = 534, P < 0.001) and (B)

The ME population infected by *S. aureus* (N = 431, P = 0.045). *The fitted logistic regression function for each univariate relationship is shown by the black line, with the 95% confidence bands around this function shown by the grey lines. The observed proportion of successful per-patient microbiological response among patients with free-drug % T > MIC < 100 in three groups of equal number of patients is shown by the dashed lines. Each fitted functions is overlaid on a histogram showing the population-specific distribution of free-drug % T > MIC values. Source: Report ICPD 00174-6, Page 62.*

For CABP, univariate logistic regression analyses based on all evaluable patients failed to demonstrate any significant PK-PD relationships between free-drug % T > MIC and response. As the majority (>90%) of patients had free-drug % T > MIC values greater than 90%, the exposure range was not broad enough to inform a PK-PD relationship for efficacy.

Reviewer's comment*: The sponsor's approach to provide empirical Bayesian estimates of ceftaroline plasma concentration and derive free-drug % T>MIC for individuals in the ME population who did not have PK sample taken is reasonable. The reviewer used the similar approach to assess the exposure-response relationship for the ME population* infected by either *S. aureus* or *S. pyogenes, or both. The sponsor's conclusion regarding the lack of significant PK-PD relationship between free-drug % T > MIC and response in CABP patients due to high target attainment is reasonable.*

4 REVIEWER'S ANALYSIS

4.1 Introduction

The reviewer explored the relationship between the ceftaroline exposure observed in the patients and the demographic factors including body weight, age, gender, and race to evaluate the pertinent label claims. In addition, in light of that the sponsor discovered an error (i.e., a wrong molecular weight conversion factor was used for ceftaroline) in the population PK analysis after the NDA submission and claimed that the population analysis remain unaffected by this error, the reviewer ran independent analysis to verify if the resultant PK exposure estimates remains unaffected and if the exposure-response analysis needs to be re-assessed.

In the exposure-response analysis in cSSSI patients, the sponsor focused on two populations, the total ME population and the ME patients infected by *S. aureus.* Because both *S. aureus* and *S. pyogenes* are the common pathogens in cSSSI patients, the reviewer conducted the exposure-response analysis, focusing on the ME patients infected by either *S. aureus* or *S. pyogenes,* or both.

4.2 Objectives

The objectives of the analysis are therefore:

1. To assess the sponsor's population PK analysis.
2. To explore the potential correlations between the ceftaroline exposure (i.e. AUCτ) and the demographic factors including body weight, age, gender, and race in the patient population.
3. To explore the exposure-response relationship in the cSSSI ME population and to identify if there are predictors of low microbiological response to ceftaroline other than the free drug %T>MIC.
4. To assess if the ceftaroline exposure data obtained from patients support the proposed dose adjustment based on renal function.

4.3 Methods

Population PK analysis was conducted using NONMEM® VI and R. Logistic regression, proportion test and plotting were performed using R and S-Plus. The free-drug %T>MIC was used as the indicator for ceftaroline exposure in the exposure-response analysis. Only the individuals who had PK data were included in the analysis to estimate AUCτ using the population PK model and to assess the effects of the demographic factors on ceftaroline exposure.

4.3.1 Data Sets

Data sets used are summarized in **Table 3.**

Table 3: Analysis Data Sets

Study Number	Name	Link to EDR
ICPD 00174-3	actp123.xpt	\\cdsesub1\evsprod\NDA200327\0000\m5\datasets\00174-3\analysis\actp123.xpt
ICPD 00174-4	capact.xpt	\\cdsesub1\evsprod\NDA200327\0000\m5\datasets\00174-4\analysis\capact.xpt
ICPD 00174-6	pkpdskin.xpt	\\cdsesub1\evsprod\NDA200327\0000\m5\datasets\00174-6\analysis\pkpdskin.xpt
ICPD 00174-7	pkpd_cap.xpt	\\cdsesub1\evsprod\NDA200327\0000\m5\datasets\00174-7\analysis\pkpd_cap.xpt

4.3.2 Software

NONMEM® VI, R, and SAS.

4.4 Results

4.4.1 Population PK Analysis

The analysis was performed in NONMEM using the corrected dataset (sact2.csv derived from actp123.xpt; capact1.csv derived from actcap.xpt) and the sponsor's population PK model. The NONMEM output is in agreement with what the sponsor reported. Basic goodness-of-fit diagnostic plots support the sponsor's PK model (**Figure 10**). Therefore, the resultant PK exposure and free-drug %T>MIC estimates remains unaffected and there is no need to modify the dataset used for exposure-response analysis.

4.4.1.1 The effect of age on ceftaroline exposure

As shown in **Figure 12**, ceftaroline exposure measured by the mean AUCτ in the cSSSI PK population was approximately 80% higher in patients ≥ 65 years of age than that of the patients < 65 years of age (95.4 mg• hr/L *vs.* 53.1 mg• hr/L). These five patients all had mild renal impairment and received no dose adjustment. Assuming there are two patients: one is 30 year-old with CrCL at 80 mL/min, the other is of the older age at 65 but with a lower CrCL at 30 mL/min. AUCτ for the older patient is estimated by the population PK model to be 80% higher than that in the patient of 30 years of age. Given the differences in both age (75 *vs* 40) and CrCL (68 mL/min *vs* 107 mL/min) for the two cSSSI PK subgroups depicted in **Figure 14**, an 80% higher AUCτ for in the elderly group is not too surprising.

As shown in **Figure 15**, ceftaroline exposure measured by the mean AUCτ in CABP PK population was approximately 18% higher in patients ≥ 65 years of age than that of the patients < 65 years of age (78.5 mg• hr/L *vs.* 66.8 mg•hr/L).

Because the adverse event profiles in patients ≥ 65 years of age and in patients < 65 years of age enrolled in the clinical studies (n=1305) were similar (**Table 4**), despite a higher exposure observed in the elderly patients, further dose adjustment based on age (in addition to the proposed dose adjustment based on renal function) is not warranted for the cSSSI or CABP patients ≥ 65 years of age.

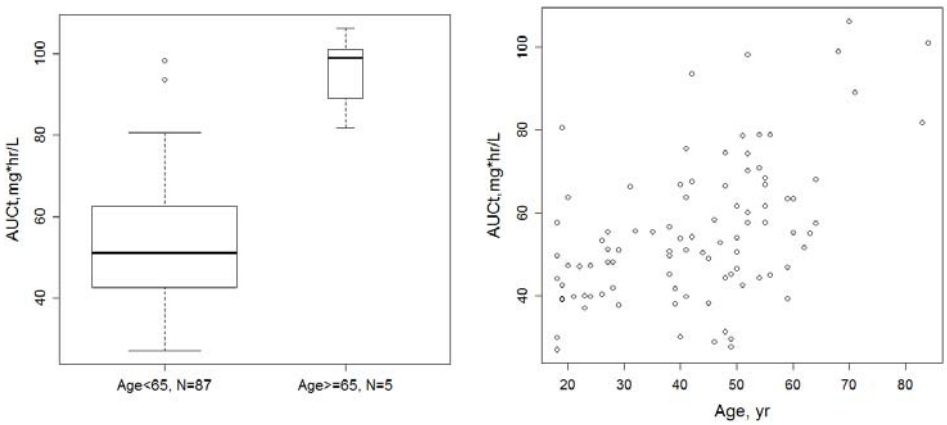


Figure 14: The boxplot (Left) and scatter plot (Right) of the estimated ceftaroline AUCτ with age in cSSSI PK population. The cSSSI PK population includes n=92 patients in Study P903-03(Phase 2), P903-06(Phase 3) and P903-07(Phase 3). All of these patients received 600 mg q12h doses

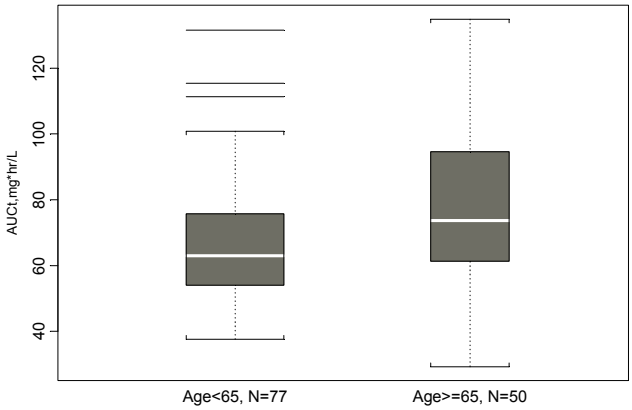


Figure 15: The estimated ceftaroline AUCτ under two age groups in CABP PK population. *The CABP PK population includes n=127 patients in P903-08(Phase 3) and P903-09 (Phase 3). Patients received either 600 mg q12h doses or 400 mg q12h when 30 mL/min < CrCL < 50 mL/min*

Table 4: Incidences of some common (>3%) treatment-emergent adverse events in CSSSI and CABP safety population (n=1305) in two age groups: Age ≤65 *vs.* Age >65

Years of age	Diarrhea	Nausea	Headache
Age ≤65	43/908(5%)	42/908(5%)	43/908(5%)
Age >65	17/397(4%)	13/397(3%)	14/397(4%)

4.4.1.2 The effect of body weight on ceftaroline exposure

As shown in **Figure 16**, no significant trend can be observed between the body weight and ceftaroline exposure measured by AUCτ in patient PK population.

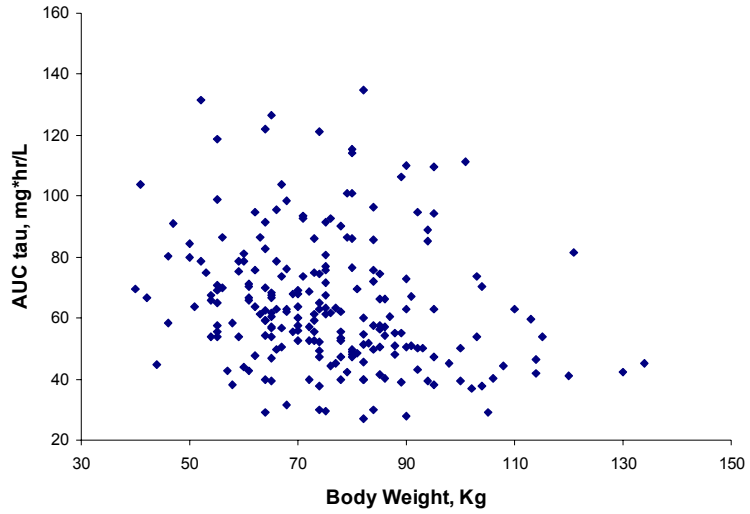


Figure 16: The scatter plot for the estimated ceftaroline AUCτ and body weight in cSSSI PK (n=92) and CABP PK populations (n=127)

4.4.1.3 The effect of race on ceftaroline exposure

The effect of race on ceftaroline exposure was assessed based on ceftaroline AUCτ values in cSSSI PK population **(Figure 17)**. ANOVA analysis showed that ceftaroline AUCτ values are not significantly different among different race groups including White, Black and Hispanic patients (*p=0.82*). In the CABP PK population, ceftaroline AUCτ values are comparable among different race groups including white (71.7 ± 21.0 mg•hr/L, n=115), Asian (67.1 ± 31.0 mg•hr/L, n= 6) and others (70.0 ± 24.0 mg•hr/L, n= 6).

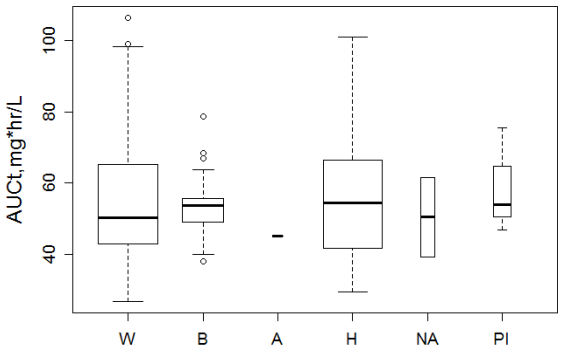


Figure 17: Ceftaroline exposure measured by AUCτ in the cSSSI PK population based on race (W=White, n=35; B=Black, n=17; A=Asian, n=1; H =Hispanic, n=34; NA=Native American, n=2; PI=Pacific Islander, n=3)

4.4.1.4 The effect of gender on ceftaroline exposure

As shown in **Figure 18**, no significant difference in ceftaroline AUCτ was observed between male and female patients in the cSSSI PK population. Similarly, no significant difference in ceftaroline AUCτ (mean ± SD) was observed between male (n=77, 69.1± 20.8 mg•hr/L) and female (n=50, 74.9 ± 22.4 mg•hr/L) patients in the CABP PK population.

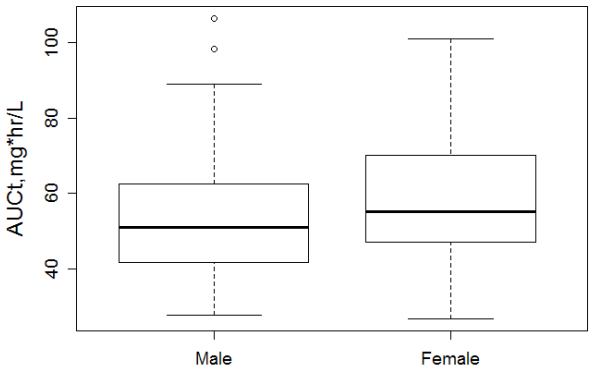


Figure 18: Ceftaroline exposure measured by AUCτ (mean ± SD) between male (n=51, 53.2 ± 16.3 mg•hr/L) and female (n=41, 58.1± 18.1 mg•hr/L) cSSSI PK patients

4.4.2 Dose adjustment based on renal function

See Section 1.1.3.

4.4.3 Exposure-Response Analysis

4.4.3.1 cSSSI

Logistic regression analysis of the free-drug %T>MIC versus the per-patient microbiological response in cSSSI patients showed a significant positive relationship. Model results are presented in **Table 5** and **Figure 2**. This relationship is in agreement with the sponsor's analysis (**Figure 13**) where the analysis populations were the total ME population and the ME population infected by *S. aureus*.

Table 5: Reviewer's Logistic Regression Analysis Parameter Estimates

Parameter	Estimate	P-value	Standard Error
%T>MIC	0.02826	0.0266	0.01275

As shown in **Figure 3**, the patients > 60 years of age, despite of a lower response rate, had a significantly higher mean steady-state AUCτ (75.2 mg•hr/L *vs.* 52.7 mg•hr/L) than the patients ≤ 60 years of age. Based on the data from a subset of patients (n= 41) in the cSSSI PK population (n=92) who also had the record on diabetes status, the AUCτ mean values are similar and independent of diabetes status (**Figure 4**). Therefore, based on the available data from a limited number of patients, the reviewer concludes that the low response in either patients ≤ 60 years of age or patients with diabetes is perhaps not due to the difference in ceftaroline plasma exposure.

4.4.3.2 CABP

For the community-acquired pneumonia (CABP), the exposure-response relationship was not identified due to target attainment in the majority of patients. Over 90% patients in the ME population with CABP had free-drug %T>MIC greater than 90%, therefore, the exposure range was not broad enough to inform an exposure-efficacy relationship. However, the target attainment (i.e. %T>MIC greater than 40%) achieved in all the patients infected by *S. pneumoniae* supports the proposed dose (600 mg q12h) for CABP.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
run22 mod; run22.lst	Final population PK NONMEM model and output	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\PPK Analyses \Final Model
Exposure_demog.R	Derive AUCτ in cSSSI patients and explore the relationship between AUCτ and demographic covariates	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\PPK Analyses\CSSSi
Exposure_demog_CABP.R	Derive AUCτ in CAP patients and explore the relationship between AUCτ and demographic covariates	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\PPK Analyses\CABP
Format_cSSSI_dada.R	Subset cSSSI data to prepare for E-R analysis; Reviewer's logistic regression analysis	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\ER Analyses\CSSSI
Format_CABP_dada.R	Subset CABP data to prepare for E-R analysis	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\ER Analyses\CABP
cSSSI_logreg_final.R	Generate the logistic regression graph: %T>MIC *vs.* Per-patient microbiological response in CSSSI patients	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\ER Analyses\CSSSI
run12 mod; run12.lst	Estimate AUC using the Pop PK model (cSSSI)	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\PPK Analyses\CSSSi
run3.mod; run3.lst	Estimate AUCτ using the Pop PK model (CABP)	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\PPK Analyses\CABP
Simulation_severe_400mg300mg.R	R script to generate simulation results used for dose recommendation in patients with severe renal impairment	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\PPK Analyses\Final Model\Dose simulation for severe
run4 mod run4.csv Clearance.R	NONMEM dataset, control stream, and R script to generate graphs to illustrate the contribution of linear and non-linear components to the total clearance based on the sponsor's final pop PK model	\\cdsnas\pharmacometrics\Ceftaroline_NDA200327_EZ\PPK Analyses\Final Model\
AE_age_renal function.sas	SAS script to calculate the incident of adverse events in patients based on age or renal function strata	\\cdsnas\pharmacometrics\Review\Ceftaroline_NDA200327_EZ\FDA Reviews\safety analysis

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	200-327	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	IV	**Generic Name**	Ceftaroline fosamil for Injection
Medical Division	DAIOP	**Drug Class**	Cephalosporin
OCP Reviewer	Aryun Kim, Pharm.D.	**Indication(s)**	• Complicated skin and skin structure infections (cSSSI) • Community-acquired bacterial pneumonia (CABP)
OCP Team Leader	Charles Bonapace, Pharm.D.	**Dosage Form**	Sterile powder for intravenous use
Pharmacometrics Reviewer	To be determined	**Dosing Regimen**	600 mg every 12 hours
Date of Submission	30 Dec 2009	**Route of Administration**	IV infusion
Estimated Due Date of OCP Review	30 Aug 2010	**Sponsor**	Cerexa, Inc.
Medical Division Due Date	30 Aug 2010	**Priority Classification**	Standard
PDUFA Due Date	30 Oct 2010		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	×			
Tabular Listing of All Human Studies	×			
HPK Summary	×			
Labeling	×			
Reference Bioanalytical and Analytical Methods	×			
I. Clinical Pharmacology				
Mass balance:	×	1		
Isozyme characterization:	×	4		
Blood/plasma ratio:	×	1		
Plasma protein binding:	×	2		
Pharmacokinetics (e.g., Phase I) -	×	10		
Healthy Volunteers-				
single dose:	×	10		
multiple dose:	×	4		
Patients-				
single dose:	–	–		
multiple dose:	×	6		2 Phase 2 studies 4 Phase 3 studies

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Dose proportionality -				
fasting / non-fasting single dose:	×	2		
fasting / non-fasting multiple dose:	×	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	–	–		
In-vivo effects of primary drug:	–	–		
In-vitro:	×	1		
Subpopulation studies -				
ethnicity:	–	–		
gender:	×	1		
pediatrics:	×	1		
geriatrics:	×	1		
renal impairment:	×	3		
hepatic impairment:	–	–		
PD -				
Phase 2:	×	2		
Phase 3:	×	4		
PK/PD -				
Phase 1 and/or 2, proof of concept:	×	2		Exposure-Response analyses
Phase 3 clinical trial:	×	4		Exposure-Response analyses
Population Analyses -				
Data rich:	×			
Data sparse:	×			
II. Biopharmaceutics				
Absolute bioavailability	×	1		Intramuscular administration
Relative bioavailability -	–	–		
solution as reference:	–	–		
alternate formulation as reference:	–	–		
Bioequivalence studies -	–	–		
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	–	–		
Bio-waiver request based on BCS	–	–		
BCS class	–	–		
Dissolution study to evaluate alcohol induced dose-dumping	–	–		
III. Other CPB Studies				
Genotype/phenotype studies	–	–		
Chronopharmacokinetics	–	–		
Pediatric development plan	–	–		
Literature References	×			
Total Number of Studies		17		11 Phase 1 studies 2 Phase 2 studies 4 Phase 3 studies

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			×	IV formulation

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

2	Has the applicant provided metabolism and drug-drug interaction information?	×			In vitro and in vivo metabolism data only
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			×	IV formulation
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	×			
5	Has a rationale for dose selection been submitted?	×			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	×			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	×			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	×			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	×			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			×	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	×			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		×		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	×			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	×			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			×	The Sponsor has submitted a deferral request for pediatric assessment as a Phase 4 commitment for both cSSSI and CABP indications
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			×	The Sponsor has submitted a deferral request for pediatric assessment as a Phase 4 commitment for both cSSSI and CABP indications
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology	×			

	section of the label?				
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	×			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			×	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Aryun Kim, Pharm.D.	**18 Feb 2010**
Reviewing Clinical Pharmacologist	Date
Charles Bonapace, Pharm.D.	**18 Feb 2010**
Team Leader/Supervisor	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

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

/s/

ARYUN KIM
02/18/2010

CHARLES R BONAPACE
02/19/2010