Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ceftaroline fosamil

Proprietary Product Name: Zinforo

Sponsor: AstraZeneca Pty Ltd

Date of CER:
8 April 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	adverse event
Ae	amount of unchanged drug excreted into the urine
Ae_{0-t}	cumulative amount of unchanged drug excreted into the urine from time 0 to time t
APTT	activated partial thromboplastin time
AUC_{0-t}	area under the plasma concentration versus time curve from time zero to time t
$AUC_{0-\infty}$	area under the plasma concentration versus time curve from time zero to infinity
CAP	community acquired pneumonia
CABP	community acquired bacterial pneumonia
CE	clinically evaluable
CI	confidence interval
CL	plasma clearance
CLr	renal clearance
C_{max}	maximum plasma drug concentration
cMITT	clinical modified intention to treat
CrCl	creatinine clearance
cSSTI	complicated skin and soft tissue infections (the abbreviation cSSTI (complicated skin and skin-structure infections), was originally also used in this CER)
CT	computerised tomography
CXR	chest X-ray
Bias PE%	Calculated as the population mean predicted exposure measure minus the individual predicted exposure measure multiplied by 100 and then divided by the individual predicted exposure measure
DAE	discontinuation due to adverse event

Abbreviation	Meaning
DM	diabetes mellitus
ECG	electrocardiogram
EOT	end of treatment
ESBL	extended spectrum β-lactamase
ESRD	end-stage renal disease
IM	intramuscular
IV	intravenous
IVRS	interactive voice response system
LC	Liquid chromatography
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LFU	late follow-up
ME	microbiologically evaluable
MIC	minimal inhibitory concentration
MIC90	minimal inhibitory concentration required to inhibit the growth of 90% of organisms
MITT	modified intention to treat
MITTE	modified intention to treat efficacy
mMITT	microbiological modified intention to treat
mMITTE	microbiological modified intention to treat efficacy
MRSA	methicillin-resistant Staphylococcus aureus
MSSA	methicillin susceptible Staphylococcus aureus
PBP	penicillin binding protein
PCS	potentially clinically significant
PD	pharmacodynamic
PE	predicted exposure
PK	pharmacokinetic

Abbreviation	Meaning
Precision |PE%|	Calculated as the absolute value of the PE%
PNSP	penicillin non-susceptible Streptococcus pneumoniae
PRP	Penicillinase-resistant penicillin
PRSP	penicillin resistant Streptococcus pneumoniae
PSSP	penicillin susceptible Streptococcus pneumoniae
PT	Prothrombin time
PTA	probability of target attainment
PVD	peripheral vascular disease
QT	A measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.
QTc	The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.
QTcIb	QT interval corrected for heart rate using an individual subject correction formula based on the baseline QT-RR slope
q12h	twelve hourly intervals
SAE	serious adverse event
SD	Standard deviation
Std	Standard
TEAE	treatment emergent adverse event
$T_{½}$	terminal elimination half-life
T_{max}	time of maximum plasma drug concentration
TOC	test of cure
v	Volume
VISA	vancomycin intermediate Staphylococcus aureus
VRSA	vancomycin resistant Staphylococcus aureus

1. Clinical rationale

The Sponsor provides the following rationale in support of the application:

"There remains a persistent and growing unmet medical need for new antibiotics that provide efficacy in the treatment of patients with cSSTI and CAP. cSSTIs that require hospitalization or medical attention are increasing in incidence and despite advances in medical care and antimicrobial therapy, CAP remains an important cause of mortality and hospitalization throughout the world. New antimicrobials with an enhanced spectrum of activity are needed for such serious infections, especially given the rising incidence of highly resistant and highly virulent pathogens such as MRSA, vancomycin intermediate and resistant *S. aureus* (VISA and VRSA) and MDRSP. Zinforo addresses this distinct area of unmet medical need."

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

There were five pharmacokinetic studies conducted in healthy subjects: Study P903-13, Study P903-01, Study P903-17, Study P903-20 and Study CXL-PK-01. There were five pharmacokinetic studies investigating the effects of intrinsic factors: Study P903-02, Study P903-04, Study P903-18, Study P903-15 and Study 903-11. There were eight population pharmacokinetic studies: Study P903-HP-001, Study P903-HP-002, Study P903-HP-003, Study 00174-1, Study 00174-2, Study 00174-3, Study 00174-4 and Study 00174-5.

There was one thorough QT study: Study P903-05.

There was one study of the effect of ceftaroline on enteric bacteria: Study P903-14

There were five simulation studies, using the models derived from the population pharmacokinetic studies: Study 00174-6, Study 00174-7, Study 00174-8, Study 00174-9 and a study entitled "Technical Report: Supplementary target attainment analysis for patients with infection of cSSTI and CAP".

There were two Phase II studies conducted, both for the indication of cSSTI: Study P903-03 and Study P903-19

There were two Phase III studies conducted for the indication of cSSTI: Study P903-06 and Study P903-07

There were two Phase III studies conducted for the indication of cSSTI[1]: Study P903-08 and Study P903-09

There were no additional clinical studies evaluable only for safety.

2.2. Paediatric data

The submission included paediatric pharmacokinetic data for age 12 years and older. However, the Sponsor has not applied for the indication to include paediatric patients.

[1] Erratum: CAP

2.3. Good clinical practice

All the clinical studies presented in the dossier were stated to have been conducted in accordance with Good Clinical Practice.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

There were five pharmacokinetic studies conducted in healthy subjects: Study P903-13, Study P903-01, Study P903-17, Study P903-20 and Study CXL-PK-01. There were five pharmacokinetic studies investigating the effects of intrinsic factors: Study P903-02, Study P903-04, Study P903-18, Study P903-15 and Study 903-11. There were eight population pharmacokinetic studies: Study P903-HP-001, Study P903-HP-002, Study P903-HP-003, Study 00174-1, Study 00174-2, Study 00174-3, Study 00174-4 and Study 00174-5.

3.1.1. Pharmacokinetic studies conducted in healthy subjects

Study P903-13 was a single dose, open label study to assess the metabolism and elimination of intravenously administered radio-labelled ceftaroline fosamil. The study was a mass balance study. The study included six healthy male volunteers aged 18 to 45 years. Each subject had ceftaroline 600 mg, intravenously over 30[2]minutes, with an additional 15 mg of [14C] ceftaroline fosamil. Blood, faeces and urine samples were collected over 168 hrs. Mean (SD) total recovery of drug was 93.4 (3.1) %, with recovery from urine of 87.5 (3.9%) and faeces of 5.95 (2.93%). The ceftaroline pharmacokinetic parameters are summarised in Table 1.

Table 1. Study P903-13

Mean Pharmacokinetic Parameters (± SD) for Ceftaroline, Ceftaroline Prodrug, Ceftaroline M-1, and Total Radioactivity following a Single IV infusion of [^{14}C] Ceftaroline Fosamil				
PK Parameter	*Ceftaroline (N = 6)*	*Ceftaroline Prodrug (N = 6)*	*Ceftaroline M-1 (N = 6)*	*Total Radioactivity[a] (N = 6)*
C_{max} (ng/mL)	27352.20 ± 2845.23	2018.29 ± 312.54	2156.18 ± 161.58	35783.33 ± 2906.83
AUC_{0-t} (ng•hr/mL)	63787.11 ± 6304.93	1564.85 ± 224.94	13163.16 ± 935.85	432197.99 ± 45635.78
$AUC_{0-\infty}$ (ng•hr/mL)	64217.67 ± 6379.11	NC	13669.67 ± 874.01	935735.58 ± 175792.71[a]
T_{max} (hr)[a]	0.98 (0.95-1.08)	0.67 (0.33-0.98)	0.98 (0.95-1.08)	0.98 (0.95-1.08)
$T_{½}$ (hr)	2.60 ± 0.46	NC	4.22 ± 0.33	214.61 ± 27.92 d
CL (mL/hr)	8679.47 ± 875.46	NC	41774.38 ± 2771.09	688.36 ± 124.90
V_{ss} (mL)	20117.01 ± 1366.71	NC	248184.52 ± 12153.13	191363.44 ± 18778.19
V_z (mL)	32176.88 ± 3443.33	NC	253770.63 ± 20769.61	210129.44 ± 25886.75
Ae_{0-t} (mg)	359.36 ± 46.55	0.00	32.24 ± 6.37	547.87 ± 26.74
Ae_{0-t} (% dose)	65.02 ± 8.22[c]	0.00	5.66 ± 1.10	87.51 ± 3.94
CLr (mL/hr)	5555.61 ± 198.01[c]	0.00	2472.39 ± 590.24	1275.57 ± 100.40

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

Ceftaroline C_{max} was 27.4 μ g/mL and $AUC_{0-\infty}$ was 64.2 μ g·hr/mL. Maximum plasma concentrations of ceftaroline generally occurred just before or just after the end of study drug infusion. The mean $T_{½}$ of ceftaroline was 2.60 ± 0.46 hrs and the mean percent of dose excreted in urine as ceftaroline was approximately 65%. The systemic exposure to ceftaroline prodrug and ceftaroline M-1, as determined by AUC, were about 2.5% and 20%, respectively, of the

[2] Erratum: 60 min

systemic exposure of ceftaroline. Ceftaroline prodrug was eliminated rapidly, it was not measurable in plasma by 30 minutes after the end of study drug infusion and there was no measurable ceftaroline prodrug in any of the urine samples collected. The mean T½ of ceftaroline M-1 was 4.22 ± 0.33 hrs. The mean percent of dose excreted in urine as ceftaroline M-1 was 5.66% ± 1.10%.

Study P903-01 was a single centre, randomised, double blind, placebo controlled, Phase I, dose escalation study to determine the safety, tolerability and pharmacokinetics of ceftaroline fosamil in healthy subjects. The study was designed in two parts:

- Part 1: ceftaroline fosamil single dose, ascending regimen of 50, 100, 250, 500, 750 and 1000 mg
- Part 2: ceftaroline fosamil 300 mg q12h for 14 days, 600 mg q12h for 14 days and 800 mg q24h for 7 days

All doses were administered intravenously over 60 minutes. There were 48 volunteers in Part 1 (36 treated with ceftaroline fosamil); and 24 volunteers in Part 2 (18 treated with ceftaroline fosamil). All subjects were male and the age range 19 to 54 years. The Pharmacokinetic data were not provided in the study report.[3]

Study P903-17 was a randomised, two-part, single and multiple dose study to determine the safety, tolerability and pharmacokinetics of ceftaroline fosamil administered by intramuscular injection in healthy subjects. In Part A there was four treatment groups:

- 400 mg (228 mg/mL) ceftaroline fosamil, intramuscular administration on Day 1
- 600 mg (165 mg/mL) intramuscular administration on Day 1
- 600 mg (228 mg/mL) intramuscular administration on Day 1 and 600 mg intravenous administration on Day 8
- 1000 mg (228 mg/mL) intramuscular administration on Day 1

In Part B there were two treatment groups:

- 600 mg ceftaroline fosamil, intramuscular administration q12h for 5 days
- 1000 mg cefepime, intramuscular administration q12h for 5 days

There were 24 subjects enrolled in Part A: 17 male, seven female and the age range was 19 to 44 years. There were 18 subjects enrolled in Part B: 14 males, four females and the age range was 18 to 41 years.

For single doses, in the dose range 400 mg to 1000 mg, clearance was approximately 6 L/h and did not differ significantly between the dose levels. There was greater absorption for the 165 mg/mL than the 228 mg/mL concentration: with Cmax and AUC values being approximately 72% and 56% greater, respectively. For the 228 mg/mL concentration, Cmax and AUC were dose-proportional. The mean (SD) bioavailability of the IM dose was 107.38 (7.1) %. T_{max} was 1.5 to 2 hr for intramuscular dosing.

For ceftaroline, the multiple dosing data did not indicate either accumulation, or induction of clearance (Table 2). There was no accumulation of either pro-drug or the M-1 metabolite.

[3] Sponsor correction: The PK data were included in the submission.

Table 2. Pharmacokinetic Parameters (Mean ± SD) for Ceftaroline Following Single and Multiple Intramuscular Injections of 600-mg Ceftaroline Fosamil q12h

PK Parameter	*Treatment E, Day 1 600 mg IM (228 mg/mL) (N = 12)*	*Treatment E, Day 5 600 mg IM, q12h (228 mg/mL) (N = 12)*
C_{max}, ng/mL	11557.40 ± 3416.47	12960.27 ± 1360.85
C_{min}, ng/mL	824.57 ± 502.39	613.99 ± 206.81
C_{av}, ng/mL	NA	5450.62 ± 983.95
$AUC_{0-\tau}$, ng•h/mL	55289.45 ± 11,076.39	65407.43 ± 11,807.40
T_{max}, h[a]	2.0 (1.0-2.02)	2.0 (1.0-2.02)
$T_{½}$, h	2.54 ± 0.63	2.51 ± 0.45
Accumulation index	NA	1.20 ± 0.18
Fluctuation	NA	2.33 ± 0.56
Swing	NA	27.90 ± 30.78
Ae_{0-t}, mg	361.42 ± 69.44	371.59 ± 86.75
Ae_{0-t}, % dose	68.22 ± 13.11	70.14 ± 16.37
CL_r, mL/h	6620.15 ± 936.10	5711.89 ± 1257.65

a Median (min-max)

Ae = amount of unchanged drug excreted into the urine; Ae_{0-t} = cumulative amount of unchanged drug excreted into the urine from time 0 to time t; $AUC_{0-\tau}$ = area under the plasma concentration versus time curve during the dosing interval, τ; C_{av} = average plasma drug concentration; CL_r = renal clearance; C_{max} = maximum plasma drug concentration; C_{min} = minimum plasma drug concentration; IM = intramuscular; NA = not applicable; PK = pharmacokinetic; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma drug concentration.

Study P903-20 was randomised, double blind, placebo controlled, Phase I study of the safety and pharmacokinetics of single and multiple dose regimens of intravenous ceftaroline in healthy subjects. The study treatments were ceftaroline fosamil:

- Cohort A1: 1500 mg single dose
- Cohort A2: 200[4] mg single dose
- Cohort B1: 600 mg as a single dose on Days 1 and 10 and as multiple doses q8h on Days 2 to 9

A fourth cohort was planned at the 1200 mg q12h dose level but no subjects were recruited. The study included 30 healthy volunteers: ten in each cohort (8 active and 2 placebo). Four subjects in the multiple dose group discontinued because of AEs. There were 17 (56.7%) females, 13 (43.3%) males and the age range was 18 to 44 years.

For ceftaroline, there was dose proportionality for Cmax and AUC across the dose range 600 mg to 2000 mg. $T_{½}$ was stable across this dose range at around 2.5 hrs, as was clearance at around 7 L/hr. Around 60% of the dose was recovered in urine as ceftaroline. Ceftaroline fosamil was rapidly converted to ceftaroline, with a $T_{½}$ of 0.16 h or less and no ceftaroline fosamil was

[4] Erratum: 2000 mg single dose

recovered in the urine (Table 3). Ceftaroline M-1 had a longer $T_{½}$ of around 4.5 hrs and there was some accumulation over the 9 days of multiple dosing (Table 4).

Table 3. Pharmacokinetic Parameters (Mean ± SD) for Ceftaroline Fosamil Following Intravenous Infusion of Ceftaroline Fosamil

PK Parameter	*(1500 mg Ceftaroline fosamil) (N = 8)*	*(2000 mg Ceftaroline fosamil) (N = 8)*	*(600 mg Ceftaroline fosamil q8h)*	
			Day 1 (N = 8)	*Day 10 (N = 4)*
AUC_{0-t}, ng • h/mL	5298.1 ± 1530.3	8346.0 ± 2784.1	1866.0 ± 377.0	2424.7 ± 561.6
$AUC_{0-\infty}$, ng • h/mL	7007.6 ± 1199.2 (n = 2)	8416.2 ± 2993.3 (n = 7)	2091.3 (n = 1)	2081.0 (n = 1)
C_{max}, ng/mL	6936.4 ± 1563.9	12238.3 ± 4623.1	2285.5 ± 493.6	2926.5 ± 622.3
T_{max}, hour[a]	0.833 (0.667-0.983)	0.825 (0.333-0.983)	0.794 (0.333-1.033)	0.871 (0.333-1.067)
$T_{½}$, h	0.163 ± 0.072 (n = 2)	0.118 ± 0.044 (n = 7)	0.061 (n = 1)	0.048 (n = 1)
CL, mL/h	217235.8 ± 37176.6 (n = 2)	252064.3 ± 85400.5 (n = 7)	286907.7 (n = 1)	288325.4 (n = 1)
V_z, mL	49097.7 ± 13890.8 (n = 2)	40993.0 ± 13585.3 (n = 7)	25266.7 (n = 1)	20142.6 (n = 1)
V_{ss}, mL	31889.9 ± 3190.7 (n = 2)	42823.4 ± 14686.1 (n = 7)	48289.8 (n = 1)	48815.4 (n = 1)
Ae_i, mg				
Predose, –2 to 0 h	0	0	0	0
0 to 2 h	0	0	0	0
> 2 to 4 h	0	0	0	0
> 4 to 8 h	0	0	0	0
> 8 to 12 h	0	0	0	0
> 12 to 24 h	0	0	0	0
> 24 to 48 h	0	0	NA	0
Ae_{0-t}, mg	0	0	0	0
Percent recovered (% dose)	0	0	0	0
CL_r, mL/h	0	0	0	0

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

a. T_{max} results are expressed as the median (minimum-maximum).

Table 4.Pharmacokinetic Parameters (Mean ± SD) for Ceftaroline M-1 Following Intravenous Infusion of Ceftaroline Fosamil

PK Parameter	*(1500 mg Ceftaroline fosamil) (N = 8)*	*(2000 mg Ceftaroline fosamil) (N = 8)*	*(600 mg Ceftaroline fosamil q8h)*	
			Day 1 (N = 8)	*Day 10 (N = 4)*
AUC_{0-t}, ng • h/mL	35300.9 ± 4248..2	44879.7 ± 6732.0	14554.3 ± 2262.4	22631.2 ± 5010.5
$AUC_{0-\infty}$, ng • h/mL	35378.6 ± 4217.6	44907.9 ± 6739.6	14864.2 ± 2271.4	22849.3 ± 5010.8
C_{max}, ng/mL	5295.0 ± 1835.3	5881.6 ± 1584.1	1789.9 ± 406.5	2481.5 ± 420.0
T_{max}, hour[a]	1.033 (0.983-1.083)	1.112 (0.983-1.500)	1.915 (1.000-3.000)	1.321 (1.133-1.500)
$T_{½}$, h	4.558 ± 0.36	4.537 ± 0.721	3.908 ± 0.632	5.684 ± 0.778
CL, mL/h	39051.7 ± 4947.9	39391.4 ± 7014.8	37501.1 ± 6086.5	24691.1 ± 5053.3
V_z, mL	257411.2 ± 44672.4	255953.1 ± 51984.1	211066.0 ± 47658.7	201732.3 ± 48495.4
V_{ss}, mL	259013.8 ± 43693.4	250128.9± 52856.6	237577.0 ± 48387.0	180108.3 ± 31321.9
Ae_i, mg				
Predose, –2 to 0 h	0	0	0	15.38 ± 5.10
0 to 2 h	32.28 ± 31.60	37.78 ± 33.20	5.51 ± 1.82	9.86 ± 2.95
> 2 to 4 h	36.75 ± 39.71	47.04 ± 46.42	6.61 ± 1.40	8.21 ± 1.47
> 4 to 8 h	61.4 ± 55.18	34.43 ± 35.24	9.20 ± 2.57	11.65 ± 4.95
> 8 to 12 h	17.87 ± 15.89	15.66 ± 7.84	5.03 ± 1.49	4.72 ± 1.29
> 12 to 24 h	10.51 ± 5.72	7.51 ± 9.19	2.04 ± 1.16	5.95 ± 1.46
> 24 to 48 h	3.42 ± 3.75	2.69 ± 1.02	NA	1.70 ± 0.31
Ae_{0-t}, mg	82.8 ± 16.4	94.6 ± 16.7	28.4 ± 5.7	42.1 ± 9.4
Percent recovered (% dose)	6.08 ± 1.20	5.49 ± 0.98	5.21 ± 1.04	7.72 ± 1.73
CL_r, mL/h	2365.1 ± 483.2	2138.3 ± 429.3	1968.6 ± 355.3	1902.3 ± 497.9

Abbreviations: Ae_i = amount of ceftaroline M-1 excreted in urine per collection interval; Ae_{0-t} = amount of ceftaroline M-1 excreted in urine during the entire urine collection period from time 0 to time t; AUC_{0-t} = area under the plasma concentration-time curve up to the time corresponding to the last measurable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; CL = plasma clearance; CL_r = renal clearance; C_{max} = maximum (peak) drug concentration in plasma; ; NA = not applicable; T_{max} = time of maximum plasma concentration; $T_{½}$ = elimination half-life; V_{ss} = volume of distribution at steady-state; V_z = volume of distribution based on the terminal phase.

a T_{max} results are expressed as the median (minimum-maximum).

Study CXL-PK-01 was a single centre, two part, randomised study to investigate the pharmacokinetics of ceftaroline and NXL104. Part A was an open, single dose crossover study. Part B was a randomised, placebo controlled, double blind, multiple dose study. The study treatments were:

Part A: single dose, crossover:

- 600 mg ceftaroline fosamil
- 600 mg NXL104
- 600 mg ceftaroline fosamil and 600 mg NXL104

Part B: parallel group:

- 600 mg ceftaroline fosamil and 600 mg NXL104 q12h

- 400 mg ceftaroline fosamil and 400 mg NXL104 q8h
- 900 mg ceftaroline fosamil and 900 mg NXL104 q12h
- 600 mg ceftaroline fosamil and 600 mg NXL104 q8h

All treatments were administered intravenously over 60 minutes. In Part A there were twelve subjects: six (50%) male, six (50%) female and the age range was 20 to 44 years. All subjects completed Part A of the study. In Part B there were 48 subjects, twelve in each group with nine active and three placebo in each group. There were 24 (50%) males, 24 (50%) females and the age range was 20 to 45 years. Two subjects treated with ceftaroline 600 mg discontinued due to AEs.

Ceftaroline C_{max} and AUC were dose proportional across the dose range 400 mg to 900 mg. $T_{½}$ was around 2.5 hr and clearance was around 8 L/hr. The mean percentage of dose recovered as ceftaroline in urine ranged from 47% to 71%. NXL104 did not alter the pharmacokinetics of ceftaroline.

3.1.2. Intrinsic factor studies

3.1.2.1. Effect of impaired renal function

Study P903-02 was an open label, pharmacokinetic, safety and tolerability study of single intravenous doses of ceftaroline fosamil in subjects with normal renal function (CrCl >80 mL minute), mild renal impairment (50 <CrCl ≤80 mL/ minute), or moderate renal impairment (30 <CrCl ≤50 mL/ minute). The study was conducted in two parts:

- Part A: ceftaroline fosamil 500 mg over 30 minutes
- Part B: ceftaroline fosamil 600 mg over 60 minutes

In Part A there were five healthy volunteers: four male, one female, with an age range of 35 to 62 years. In Part B there were 18 subjects, with six in each renal function group: nine (50%) male, nine (50%) female, with an age range of 24 to 75 years.

The pharmacokinetics of the parent drug, ceftaroline fosamil, did not alter with mild or moderate impairment of renal function. Ceftaroline AUC and C_{max} increased with impairment of renal function, with an increase of around 10% in C_{max} and 50% in AUC in moderate renal impairment. $T_{½}$ increased and clearance decreased with impairment of renal function. However there was markedly increased exposure to ceftaroline M-1 with a doubling of C_{max} and tripling of AUC with moderate renal impairment.

Study P903-04 was an open label pharmacokinetic study of single intravenous doses of ceftaroline in subjects with normal renal function (CrCl >80 mL/min) or severe renal impairment (CrCl ≤30 mL/min). CrCl was estimated using the Cockroft-Gault formula. Each subjects received ceftaroline fosamil 400 mg, administered intravenously over 60 minutes. There were six subjects with normal renal function: five male, one female, with an age range of 51 to 79 years. There were six subjects with impaired renal function: five males, one female, with an age range of 52 to 74 years. The subjects with normal renal function were matched by age, gender and weight to those with severe renal impairment.

In severe renal failure ceftaroline C_{max} increased by approximately 21% and AUC by 16%[5]. $T_{½}$ increased by 67% and clearance decreased by 53%. There was no significant change in T_{max}. The proportion of total dose recovered in urine as ceftaroline decreased from 62% to 23%. Ceftaroline fosamil C_{max} increased by 65% and AUC increased by 104% but only a small proportion of the total dose was recovered in urine as ceftaroline fosamil: 0.1%. Ceftaroline M-1

[5] Erratum: 115%

C_{max} increased by 120%, AUC increased by 300% and $T_{½}$ by 60%. Clearance of ceftaroline M-1 decreased by 74% and the proportion of total dose recovered in urine as ceftaroline M-1 decreased from 6% to 4%.

Study P903-18 was an open label pharmacokinetic study of single intravenous doses of ceftaroline in subjects with normal renal function and with end-stage renal disease (ESRD) on intermittent haemodialysis. The study treatment was ceftaroline fosamil 400 mg intravenously over 60 minutes. Subjects with normal renal function received one dose. Subjects with ESRD received one dose 4 hr prior to dialysis and a second dose 1 hr after dialysis, with a 7 day washout period between doses. There were six male subjects with normal renal function aged 35 to 58 years. There were six male subjects with ESRD aged 38 to 56 years. The subjects with normal renal function were matched by age, gender and weight to those with ESRD.

The pre-dialysis ceftaroline C_{max} in the subjects with ESRD was similar to that of normal subjects but AUC was doubled. Administration post-dialysis resulted in a 67%[6] increase in C_{max} and a 164% increase in AUC. Clearance of ceftaroline was decreased by 63% in ESRD. The C_{max} and AUC of ceftaroline fosamil were greatly increased in ESRD and more so with post-dialysis administration. Clearance of ceftaroline fosamil was decreased by 50[7]% with pre-dialysis administration and by 90%[8] with post-dialysis administration. The C_{max} and AUC of ceftaroline M-1 were increased by 82% and 238%[9] respectively with pre-dialysis administration and 195% and 600%[10] respectively with post-dialysis administration. Clearance of ceftaroline M-1 was decreased by 70% with pre-dialysis administration and by 85% with post-dialysis administration.

3.1.2.2. Effect of age

Study 903-11 was an open label, pharmacokinetic study of single intravenous doses of ceftaroline fosamil in healthy elderly (≥65 years of age with at least eight subjects ≥75 years of age) and healthy young subjects (18 to 45 years of age). The study treatment was ceftaroline 600 mg by intravenous infusion over 60 minutes. There were a total of 33 subjects enrolled in the study. There were 17 healthy elderly subjects: ten (58.8%) male, seven (41.2%) female, with an age range 65 to 81 years. One healthy elderly subject withdrew because of poor venous access. There were 16 healthy young subjects: ten (62.5%) female, six (37.5%) male, with an age range 19 to 44 years.

Ceftaroline C_{max} was similar for the two groups but AUC was increased by 33% in the elderly group. Ceftaroline clearance was decreased by 32%. Ceftaroline fosamil pharmacokinetic parameters were similar for the two groups. Ceftaroline M-1 Cmax and AUC were increased by 11% and 48% respectively. Ceftaroline M-1 clearance was decreased by 32%.

Study P903-15 was a multicentre, open label, non-comparative pharmacokinetic study of single intravenous dose ceftaroline fosamil in adolescent subjects aged 12 to 17 years. The study treatment was ceftaroline fosamil 8 mg/kg for subjects weighing <75 kg and 600 mg for subjects weighting ≥75 kg. The study included nine subjects who were admitted to hospital and received intravenous antibiotics. There were five males, four females and the age range was 12 to 16 years. Eight subjects were included in the pharmacokinetic analysis. Ceftaroline mean C_{max} was approximately 15.3 µg/mL, AUC was 38.9 µg.h/mL, $t_{½}$[11] was 0.95 h and clearance was 14 L/h. Ceftaroline fosamil mean $T_{½}$[12] was 0.5 h. Ceftaroline M-1 clearance was relatively rapid at 44.2 L/h, C_{max} was 2.1 µg/mL, AUC was 11.2 µg•h/mL and $T_{½}$ was 3.26 h. The mean steady state

[6] Erratum: 77%
[7] Erratum: 56%
[8] Erratum: 99%
[9] Erratum: 228%
[10] Erratum: 578%
[11] Erratum: T_{max}
[12] Erratum: T_{max}

volume of distribution of ceftaroline M-1 was much greater than that for ceftaroline: 240.6[13] L compared with 25.3[14] L.[15]

3.1.3. Population pharmacokinetic studies:

Study P0903-HP-001 was a population pharmacokinetic report of ceftaroline in healthy subjects with normal renal function and subjects with impaired renal function that combined data from Study P903-01 and Study 903-02. The study included 1598 samples from 77 subjects: 67 male and ten female. The aim was to explore the influences of covariates such as dose, weight, gender, age and renal function upon the pharmacokinetic parameters of ceftaroline and to simulate the PKPD relationship of ceftaroline. The subjects received ceftaroline fosamil in single doses of 50, 100, 250, 500, 750 and 1000 mg; multiple doses of 300 mg q12h for 14 days, 600 mg q12h for 14 days and 800 mg q24h for 7 days; and in the study of subjects with renal impairment 600 mg as a single 60-minute infusion. NONMEM version V was used for the modelling and simulation. The main covariate influencing the renal clearance of ceftaroline was CrCl. The main influence on volume of distribution was body weight. The simulations predicted that for subjects with normal renal function and for a microbe with a MIC of 2 μg/mL (free drug), the mean %T>MIC was 48% for a dose regimen of 600 mg q12h. Using an estimated CV% of 30% (which was conservative) 89% of subjects would achieve 35% T>MIC and 77% would achieve 40% T>MIC. (For a cephalosporin the target %T>MIC is 30% to 40%).

Study P903-HP-002 was a population pharmacokinetic analysis of ceftaroline in patients and healthy subjects with normal renal function and with impaired renal function, using data from Study P903-01, P903-02 and P903-03. The analysis drew heavily upon that of Study P0903-HP-001. Ceftaroline fosamil was administered in single doses of 50, 100, 250, 500, 750 and 1000 mg, multiple doses of 300 mg q12h for 14 days, 600 mg q12h for 14 days and 800 mg q24h for 7 days, as a single 60-minute infusion of 600 mg to three cohorts of six subjects each with normal renal function, or mild or moderate renal impairment and 600 mg q12h for subjects with cSSTI. The study combined the data from Study P903-01, Study 903-02 and Study 903-03. There were 1794 samples from 127 subjects. A two-compartment PK model with zero-order input and first-order elimination was used. NONMEM version 5 was used for the analysis. The PK parameters are summarised in Table 5. The simulations predicted that for subjects with normal renal function and for a microbe with a MIC of 2 μg/mL (free drug), 98% of subjects would achieve 35% T>MIC and 90% would achieve 40% T>MIC (Table 5).

[13] Erratum: 214 L

[14] Erratum: 43 L

[15] Sponsor clarification: "However, with excluding a subject with unusual low plasma concentration of ceftaroline and unusually high plasma concentrations of ceftaroline M-1, the mean ceftaroline clearance is 9.4 L/h, only slightly higher than that for adults."

Table 5. Population pharmacokinetic analysis. Study P903-HP-002

Parameters	Mean [a]	BSV (%)[b]	BOV (%)[c]
CL_r (L/hr) [d,f]	3.76 (9)	21 (14)	6.7 FIXED
CL_m (L/hr) [d,f]	4.47 (7)	-	-
V1 (L) [e,f]	17.3 (3)	26 (16)	12 FIXED
V2 (L) [e,g]	4.89 (5)	40 (19)	13.0 FIXED
Q (L/hr) [g]	1.83 (6)	58 (25)	12.4 FIXED
Effect of WT on V1	0.158 (70)	-	-
Effect of WT on V2	0.334 (41)	-	-
Effect of Dose on CL [d]	-0.068 (37)	-	-
Effect of STUDY on F1	-0.168 (8)	-	-

Source: Appendix 2
Additive residual error 0.165
[a] Parameter precision is expressed as coefficient of variation (% CV).
[b] BSV = between-subject variability, calculated as $(\text{variance})^{1/2}*100\%$, and its precision as % CV.
[c] BOV = between-occasion variability, calculated as $(\text{variance})^{1/2}*100\%$, and its precision as % CV.
[d] CL (L/hr) = 3.76* (CRCL/110) + 4.47.
[e] V1 (L)= $17.3*(WT/70)^{0.158}$; V2 (L) = $4.89*(WT/70)^{0.334}$.
[f] Correlation between CL and V1 is 0.91, calculated as $\text{covariance}_{12} \div (\text{variance}_1*\text{variance}_2)^{1/2}*100$, where variance_1 and variance_2 are variances of random effects for the two parameters and covariance_{12} is their covariance.
[g] Correlation between V2 and Q is 0.95.

Study P903-HP-003 was a simulation study of ceftaroline PK in support of dosage adjustment in renal impairment. The simulations used the PK model and parameters estimated from Study P903-HP-001. The simulations indicated that:

- In mild renal impairment (CrCl >50–80 mL/min) no dosage adjustment was necessary (600 mg q12h administered over 1 hr)
- In moderate renal impairment (CrCl >30–50 mL/min) the dose should be adjusted to 400 mg q12h, administered over 1 hr
- In severe renal impairment (CrCl ≤ 30 mL/min) no formal dosage adjustment was proposed but dose adjustment to 300 mg q12h over 1 hr may be adequate.

Study 00174-1 was a population pharmacokinetic analysis of ceftaroline fosamil and ceftaroline in healthy Phase I subjects. An errata report was provided to assess the impact of an incorrect molecular weight conversion in the original population pharmacokinetic study. Hence the errata report has been evaluated for the purposes of the current application. The doses of ceftaroline fosamil administered were: 50 mg to 2000 mg, IV or IM administration, single and multiple doses. The study used data from Study P903-01, Study P903-02, Study P903-17 and Study P903-20. The studies included healthy subjects with normal renal function between the ages of 18 and 62 years. There were 116 subjects, 983 ceftaroline fosamil concentrations and 2018 ceftaroline concentrations. Modelling was performed using NONMEM version 6. The pharmacokinetic (structural) model was more complex than the previous pop-PKPD models, as per Study P903-HP-001, Study P903-HP-002 and Study P903-HP-003. There was sequential modelling of the PK of ceftaroline fosamil and ceftaroline. Ceftaroline fosamil fitted a three compartment model and ceftaroline a two compartment. The non-renal clearance of ceftaroline was fitted to a Michaelis-Menten model.[16] The estimates of the pharmacokinetic parameters of ceftaroline fosamil are displayed in Table 6. The estimates of the pharmacokinetic parameters of ceftaroline are displayed in Table 7. Whilst the model is interesting it is not clear that a saturable non-renal[17] elimination of ceftaroline is supported by the individual subject Phase I data. In particular, the %Ae does not appear to increase with dose. Also, a three compartment

[16] Erratum: The clearance of ceftaroline was fitted to a parallel first order and a Michaelis-Menten elimination model.
[17] Erratum: Michaelis-Menten elimination

model for ceftaroline fosamil is not apparent from the individual Phase I data. However, the simultaneous modelling of ceftaroline fosamil and ceftaroline concentrations does make sense, as it clarified the input kinetics for ceftaroline and is a strength of the study design.

Table 6. Final parameter estimates and their associated precision (%SEM) for the fit of the final population PK model for ceftaroline fosamil

Parameter	Final Estimate	%SEM
ka (hr^{-1})	0.594	7.63
CL_p (L/hr)	233	2.82
Vc_p(L)	10.4	7.38
$CLd1_p$ (L/hr)	18.3	12.8
$Vp1_p$ (L)	186	22.4
$CLd2_p$ (L/hr)	18.1	16.7
$Vp2_p$ (L)	3.16	6.94
IM Bioavailability, F	1.27	4.19
FRC	0.781	4.18
ALAG4 (hr)	0.459	7.80
ω^2_{ka}	0.0654 (25.6% CV)	47.1
ω^2_{CLp}	0.0447 (21.1% CV)	19.4
ω^2_{Vcp}	0.222 (47.1% CV)	25.6
ω^2_{CLd1p}	0.228 (47.7% CV)	45.7
σ^2	0.110 (33.2% CV)	5.09

Table 7. Estimates of the pharmacokinetic parameters of ceftaroline. Population pharmacokinetic analysis. Study 00174-1

Parameter	Final Estimate	%SEM
V_{max} (mg/hr)	385	20.3
k_m (mg/L)	28.0	20.2
Vc (L)	12.1	6.19
CLd (L/hr)	20.8	8.82
Vp (L)	17.4	4.16
k_{lin} (hr^{-1})	0.253	39.8
ω^2_{Vmax}	0.0417 (20.4% CV)	18.6
ω^2_{Vc}	0.212 (46.0% CV)	42.3
ω^2_{CLd}	0.111 (33.3% CV)	27.4
ω^2_{Vp}	0.0377 (19.4% CV)	20.3
σ^2_{slp} [a]	0.0422	11.0
σ^2_{int}	0.0007	31.0

a. Residual variability expressed as a percent coefficient of variation for various predicted concentrations was 73.5% at 0.05 µg/mL, 47.0% at 0.1 µg/mL, 23.2% at 1 µg/mL, and 20.6% for concentrations > 25 µg/mL using the additive plus proportional error model

Study 00174-2 was a population pharmacokinetic analysis of ceftaroline fosamil and ceftaroline in healthy Phase I subjects and those with renal impairment. The study followed on from Study 00174-1 and the Sponsor also provided an errata report that was performed to assess the impact of an incorrect molecular weight conversion in the first version of the population pharmacokinetic study. The doses of ceftaroline fosamil used in the study were: 50 mg to 2000 mg, IV or IM administration, single and multiple doses. The study used the same methods and structural model as used in Study 00174-1. Healthy subject data were obtained from Study P903-01, Study P903-02, Study P903-17 and Study P903-20. Data from subjects with impaired renal function were obtained from Study P904-04, Study P903-11 and Study P903-18. There were 185 subjects, 1339 ceftaroline fosamil concentrations and 3028 ceftaroline

concentrations. In the covariate (final) model the Michaelis-Menten elimination of ceftaroline was related to CrCl which suggested that renal, rather than non-renal elimination was being modelled. [18] This might suggest renal secretion of ceftaroline was an important mechanism of elimination. The elimination of ceftaroline fosamil was also related to CrCl.

Study 00174-3 was a population pharmacokinetic analyses of ceftaroline fosamil and ceftaroline in Phase I subjects and subjects with complicated skin and skin-structure infections. Ceftaroline fosamil was administered in doses of 50 mg to 2000 mg, IV or IM administration, single and multiple doses. The data were modelling using NONMEM version 6. The pharmacokinetic (structural) model was the same as that developed in Study 00174-01. Phase I data were obtained from Study P903-01, Study P903-02, Study P903-04, Study P903-11, Study P903-17, Study P903-18 and Study P903-20. Phase II data were obtained from Study P903-03, Study P903-06 and Study P903-07. There were 277 subjects, 1500 ceftaroline fosamil concentrations and 3458 ceftaroline concentrations. There was a shift in the central volume of distribution of ceftaroline fosamil of 5.21 L in the Phase II/III subjects. For ceftaroline, there was an increase in the central volume of distribution of 8.97 L (1.81 fold) and of peripheral volume of distribution of 3.65 L in the Phase II/III subjects. There was an increase in clearance of 5.24 L/h (1.36 fold) in the Phase II/III subjects.

Study 00174-4 was a population pharmacokinetic study of ceftaroline fosamil and ceftaroline in Phase III patients with community acquired pneumonia. The study was a validation step using Phase III CAP data to assess predictive performance. The model used was that previously developed in Study 00174-3. The doses used in the study population were two consecutive IV infusions of either 200 mg (for patients with $30 < CrCL \leq 50$ mL/min) or 300 mg (for patients with CrCL > 50 mL) over 1 hr for 5 to 7 days. The Phase III data were obtained from Study P903-08 and Study P903-09. The data were obtained from 128 subjects and included 82 ceftaroline fosamil concentrations and 476 ceftaroline concentrations. The study used NONMEM version 6 to simulate the data, using the previously developed model and the final parameter estimates from Study 00174-3. The plot of predicted concentration and observed concentration indicated a tendency for the model to under-estimate. The median bias and precision for C_{max} were -8.28% and 14.0%, respectively; and for AUC_{0-12} were -6.22% and 16.9% respectively, indicating that the population mean predictions of ceftaroline C_{max} and AUC_{0-12} were under-predicted by the model. The population from the Phase III studies in CAP may have slightly different mean pharmacokinetic parameters to those used to develop the model. This may be significant when using the model to predict %T>MIC in later pharmacodynamic models of ceftaroline in CAP. The model may under-predict %T>MIC in this patient group.

Study 00174-5 was a population pharmacokinetic study to assess pharmacokinetic interactions of ceftaroline with concomitant medications administered to patients with complicated skin and skin structure infections or community acquired pneumonia. Using the model developed in Study 00174-3, posterior Bayesian estimates of C_{max} and AUC were calculated using the data from patients with cSSTI and CAP. Data from patients with cSSTI were obtained from Study P903-03, Study P903-06 and Study P903-07. Data from patients with CAP were obtained from Study P903-08 and Study P903-09. The doses of ceftaroline administered ranged from 200 mg to 600 mg q12h IV. Concomitant medications were categorized according to whether the agent was known to be a substrate, inhibitor, or inducer of the major cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5/7). Anionic or cationic medications known to undergo active secretion in the renal tubules were also evaluated as separate categories in addition to those medications which may potentially either increase or decrease renal blood flow or glomerular filtration rate. The posterior Bayesian estimates of AUC were plotted against the categorical variables representing exposure/non-exposure to the

[18] Sponsor clarification: "In the covariate (final) model both the linear and the Michaelis-Menten elimination of ceftaroline was related to CrCl."

different drug classes. There was an increase in AUC of up to 20% for subjects treated with CYP1A2 inhibitors, CYP3A4/5/7 inhibitors, anions undergoing active renal secretion and vasodilator drugs that may increase renal blood flow. However, for all of these drug classes median CrCl was lower and median age higher, in the exposed group. Further to this, a decrease in AUC rather than an increase would be predicted with concomitant treatment. Hence, these associations appear to be due to confounding rather than a true effect. [information redacted] As exposure to drug classes was not included in the model, the effect of these exposures is unlikely to be apparent in the posterior Bayesian estimates. Hence the study contributes little additional information regarding concomitant drug exposures and is exploratory (hypothesis generating) rather than hypothesis testing.

3.2. Summary of pharmacokinetics

Mean (SD) total recovery of intravenously administered ceftaroline fosamil is 93.4% (3.1%), with recovery from urine of 87.5% (3.9%) and faeces of 5.95 (2.93%). The mean percent of dose excreted in urine as ceftaroline is approximately 65%. Systemic exposure to ceftaroline prodrug and ceftaroline M-1, as determined by AUC, is about 2.5% and 20%, respectively, of the systemic exposure of ceftaroline.

The pharmacokinetics of ceftaroline fosamil administered intramuscularly were dose proportion at a concentration of 228 mg/mL, with a T_{max} of 1.5 to 2 hrs.

For intravenous ceftaroline fosamil there was dose proportionality for C_{max} and AUC across the dose range 600 mg to 2000 mg. $T_{½}$ was stable across this dose range at around 2.5 hr, as was clearance at around 7 L/hr.

Ceftaroline AUC and C_{max} increased with impairment of renal function, with an increase of around 10% in C_{max} and 50% in AUC in moderate renal impairment. In severe renal failure ceftaroline C_{max} increased by approximately 21%, AUC increased by 16%[19], $t_{½}$ increased by 67% and clearance decreased by 53%. Clearance of ceftaroline was decreased by 63% in ESRD. Clearance of ceftaroline fosamil was decreased by 50% with pre-dialysis administration and by 90% with post-dialysis administration. There was markedly increased exposure to ceftaroline M-1 with a doubling of C_{max} and tripling of AUC with moderate renal impairment. In severe renal failure, Ceftaroline M-1 C_{max} increased by 120%, AUC increased by 300%, $t_{½}$ increased by 60% and clearance decreased by 74%.
In healthy elderly subjects (age ≥65 years) ceftaroline C_{max} was similar to that for healthy young subjects but AUC was increased by 33% in the elderly group and ceftaroline clearance was decreased by 32%. In adolescent subjects clearance was increased to 14 L/h.

In the population pharmacokinetic studies, the main covariate influencing the renal clearance of ceftaroline was CrCl and the main influence on volume of distribution was body weight. Simulations predicted that in mild renal impairment (CrCl >50–80 mL/min) no dosage adjustment was necessary (600 mg q12h administered over 1 hr); in moderate renal impairment (CrCl >30–50 mL/min) the dose should be adjusted to 400 mg q12h, administered over 1 hr; and in severe renal impairment (CrCl ≤ 30 mL/min) no formal dosage adjustment was proposed but dose adjustment to 300 mg q12h over 1 hr may be adequate. For ceftaroline, there was an increase in the central volume of distribution of 8.97 L (1.81 fold) and of peripheral volume of distribution of 3.65 L in the Phase II/III subjects. There was an increase in clearance of 5.24 L/h (1.36 fold) in the Phase II/III subjects.[20]

[19] Erratum: 115%
[20] Sponsor clarification: "For ceftaroline, there was an increase in the central volume of distribution of 8.97 L (1.81 fold) in Phase II/III subjects compared to Phase I subjects and an increase of peripheral volume of distribution of 3.65 L in male subjects compared to female subjects.. There was an increase in clearance of 5.24 L/h (1.36 fold) in the Phase II/III subjects compared to Phase I subjects."

3.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of ceftaroline fosamil were adequately characterised in adult subjects. [information redacted].

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

There was one thorough QT study: Study P903-05.

There was one study of the effect of ceftaroline on enteric bacteria: Study P903-14.

There were five simulation studies, using the models derived from the population pharmacokinetic studies: Study 00174-6, Study 00174-7, Study 00174-8, Study 00174-9 and a study entitled "Technical Report: Supplementary target attainment analysis for patients with infection of cSSTI and CAP".

4.2. Summaries of the studies providing pharmacodynamic data

4.2.1. Thorough QT study

Study P903-05 was a randomised, double blind, placebo controlled, three period crossover study to evaluate the safety, pharmacokinetics and effect on the ECG of a supratherapeutic dose of ceftaroline in healthy subjects. The study treatments were:

1. Ceftaroline fosamil 1500 mg
2. Moxifloxacin 400 mg (positive control)
3. Placebo, saline (negative control)

Intravenous administration was over 60 minutes. There was a 5 day washout period between treatments. There were 54 subjects: 27 (50%) male, 27 (50%) female, age range 18 to 45 years. Mean clearance of ceftaroline was 6.6 L/hr and $T_{½}$ was 2.59 hrs. There was no clinically significant increase in QTcIb with ceftaroline fosamil. Positive control with moxifloxacin demonstrated QTcIb prolongation of: LS mean difference (maximal at 1 hr) of 15.7 ms. One subject in the ceftaroline group, one in the placebo and 18 in the moxifloxacin had an increase in QTcIb of ≥30 ms and no subjects had an increase in QTcIb ≥60 ms.

4.2.2. Effect on enteric bacteria

Study P903-14 was a single centre, Phase I, multiple dose study to assess the effect of ceftaroline fosamil on the intestinal microflora of healthy human subjects. Pharmacokinetic parameters were also calculated. Ceftaroline fosamil 600 mg was administered by IV infusion over 60 minutes, q12h for 7 days. The study included twelve healthy volunteers: six (50%) male, six (50%) female, with an age range of 20 to 41 years. Concentrations of ceftaroline were measured in faeces (and also as a confirmatory analysis in plasma) using a bioassay (level of inhibition [zone of inhibition] of growth of Micrococcus luteus ATCC 9341 [indicator strain] on an agar plate). On Study Day 7: the plasma concentrations (as measured by bioassay) ranged from 18.0 to 29.8 mg/L (mean value 23.8 mg/L) which is consistent with the results by LCMS. There were no measurable concentrations of ceftaroline detected with the bioassay in any faecal samples collected on Study Days –1, 2, 5, 7, 9, 14, or 21. The numbers of enterococci and C. albicans were within normal limits. Median Escherichia coli counts decreased by approximately 2.0 log CFU/g of faeces from baseline to Study Day 7 and by 1.5 log CFU/g faeces from baseline to Study Day 9 with recovery to baseline counts on Study Day 14. The median values for Enterobacteriaceae did not change significantly. On Study Day 21, there were increased numbers of Klebsiella

pneumoniae in one subject and of Citrobacter species (C. braaki, C. freundii, C. koseri, C. youngae) in five subjects. From baseline to Study Day 7, there were minimally significant decreases of approximately 2.1 log CFU/g faeces in numbers of bifidobacteria and of approximately 1.7 log CFU/g faeces in numbers of lactobacilli. There was a minimally significant increase of approximately 2.0 log CFU/g faeces in numbers of Clostridia species. No impact on the median numbers of Bacteroides was seen. C. difficile strains were isolated from two subjects on Study Days 5, 7 and 9. All isolates were toxin B positive by cytotoxin assay and positive for the ToxA and ToxB genes. No strains were positive for the binary toxin gene. No isolates belonged to any known international PCR-ribotype. No clinical symptoms were observed in these subjects. No new colonizing aerobic or anaerobic bacteria with increased MICs (≥ 4 mg/L) to ceftaroline were found.

4.2.3. PKPD simulations

Study 00174-6 was a PKPD study of ceftaroline efficacy in patients with cSSTI. PK data were not available for all the study subjects. %T>MIC was simulated for all subjects using the model developed in Study 00174-3. MIC of the isolated pathogens were used for each subject. The efficacy outcome measure was response to treatment. Logistic regression was used to determine the factors associated with treatment success. Ceftaroline fosamil 400 mg to 600 mg was administered by IM or IV injection q12h. Data were obtained from Study P903-03, Study P903-19, Study P903-06 and Study P903-07. A total of 534 subjects had MIC values and plausible simulated PK profiles and of these 105 also had PK data. There were 347 (65.0%) males, 187 (35.0%) females, the age range was 18 to 71 years, the CrCl range was 38.2 to 259.9 mL/min/1.73m^2 and 177 (33.2%) had infection with MRSA. Of a total of 534 subjects, 93.3% had clinical success. Factors improving the probability of response were: age <60 years and greater free drug %T>MIC. Factors decreasing the probability of response were wound infection, presence of bacteraemia and presence of diabetes. There was a significant difference in response rate between subjects above and below 55% T%>MIC breakpoint: 64.7% (11/17) ≤54.2% and 94.0% (486/517) >54.2%, p= 0.001.

Study 00174-7 was a PKPD study of ceftaroline efficacy in patients with CAP. PK data were not available for all the study subjects. %T>MIC was simulated for all subjects using the model developed in Study 00174-3. MIC of the isolated pathogens were used for each subject. The efficacy outcome measure was response to treatment. Logistic regression was used to determine the factors associated with treatment success. Ceftaroline fosamil 300 mg was administered by IV infusion over 30 minutes, q12h. Data were obtained from Study P903-08 and Study P903-09. There were 130 subjects, of whom 124 had MIC values and 28 had both MIC values and PK data. There were 83 (66.9%) males, 44 (33.1%) females, the age range was 23 to 99 years and the CrCl range was 30.2 to 187.9 mL/min/1.73m2. The sample size was too small to detect a relationship between %T>MIC and response.

Study 00174-8 was a PKPD study using target attainment analysis to evaluate susceptibility test interpretive criteria for ceftaroline against Staphylococcus aureus. Simulations were performed using the population PK model developed in Study 00174-03 and a target %T>MIC of 55% (from Study 00174-6). A total of 8000 subjects were simulated with varying degrees of renal impairment. Doses of ceftaroline fosamil 300 mg to 600 mg IV were simulated. The study supported a PK-PD MIC cut-off value of 1 mg/L for patients without diabetes or wound infections for the following regimens by renal function category:

- Ceftaroline fosamil 600 mg every 12 hr administered to patients with normal renal function or mild renal impairment
- Ceftaroline fosamil 400 mg every 12 hr administered to patients with moderate renal impairment
- Ceftaroline fosamil 400 mg or 300 mg every 12 hr administered to patients with severe renal impairment

Study 00174-9 was a PKPD study using target attainment analysis to evaluate susceptibility test interpretive criteria for ceftaroline against Steptococcus pneumoniae. Simulations were performed using the population PK model developed in Study 00174-03 and a target %T>MIC of 35 to 45%. A total of 8000 subjects were simulated with varying degrees of renal impairment. Doses of 300 mg q12h to 800 mg q24 h IV were simulated. A PK-PD MIC cut-off value of 1 mg/L for Steptococcus pneumoniae was supported assuming free-drug %T>MIC targets ranging from 35 to 44. In patients with normal renal function or mild renal impairment, ceftaroline fosamil 600 mg administered every 12 hr, would be adequate. For patients with moderate renal impairment ceftaroline fosamil 400 mg every 12 hr would be adequate. For patients with severe renal impairment ceftaroline fosamil 400 mg or 300 mg every 12 hr would be adequate.

Technical Report: Supplementary target attainment analysis for patients with infection of cSSTI and CAP was a Probability of Target Attainment (PTA) analyses to define the PK/PD derived breakpoint, which is the MIC at which more than 90% subjects will meet the pre-defined PK/PD target. Simulations were performed using the model developed in Study 00174-3. Targets developed using European surveillance data and data from a murine model. The estimated PK/PD derived breakpoints were:

- 2 mg/L, 1 mg/L and 0.5 mg/L for bacterial stasis , 1-log kill and 2-log kill of S. aureus, respectively, based on the PK/PD targets estimated from a nonclinical murine thigh model
- 1 mg/L, 1 mg/L and 0.5 mg/L for bacterial stasis, 1-log kill and 2-log kill of S. pneumoniae based on the PK/PD targets estimated from a nonclinical murine thigh model
- 0.5 mg/L and 0.25 mg/L for bacterial stasis and 1-log kill of non-ESBL producing Enterobacteriaceae based on the PK/PD targets estimated from a nonclinical murine thigh model

The predicted PTAs for the MIC90 of European ceftaroline surveillance data are:

- At the MIC90 values of 0.25 mg/L and 2 mg/L for methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-resistant Staphylococcus aureus (MRSA) respectively, observed in European ceftaroline surveillance studies, the predicted PTAs are 100%, 100% and 99.5% for MSSA and 96.5%, 80.6% and <35% for MRSA, for stasis, 1-log and 2-log kills, respectively.
- At the MIC90 value of 0.015mg/L and 0.25 mg/L for penicillin-susceptible Streptococcus pneumoniae (PSSP) and penicillin-nonsusceptible Streptococcus pneumoniae (PNSP), respectively, observed in European ceftaroline surveillance studies, the predicted PTAs are essentially 100% for both PSSP and PNSP for stasis, 1-log and 2-log kills respectively.
- At the MIC90 value of 0.5mg/L for non-Extended-spectrum β-lactamase (ESBL) producing E. coli and K. pneumoniae observed in European ceftaroline surveillance studies, the predicted PTAs are 98% and 66.1% for stasis and 1-log kill, respectively.

4.3. Summary of pharmacodynamics

The thorough QT study did not indicate an effect of ceftaroline on QTc.

Ceftaroline did have an altering effect on the populations of enteric bacteria. It is not clear what the clinical significance of the alterations is but there is a potential for Clostridium difficile colitis to occur as an AE.

The simulation studies provided support for the dosing regimens used in the Phase III studies.

4.4. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamics of ceftaroline were adequately characterised in the clinical studies.

5. Dosage selection for the pivotal studies

The dosage selection for the pivotal studies was developed from the pharmacokinetic and pharmacodynamic studies.

6. Clinical efficacy

6.1. Clinical efficacy in cSSTI

6.1.1. Pivotal efficacy studies

6.1.1.1. Study P903-03

6.1.1.1.1. Study design, objectives, locations and dates

Study P903-03 was a multicentre, Phase II, randomised, observer blinded study to evaluate safety and efficacy of ceftaroline fosamil compared with standard therapy in adult subjects with cSSTI. The study was sponsored and conducted by Cerexa Inc. from October 2005 to May 2006 at 15 clinical sites in the US, Latin America, South Africa and Russia.

6.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Males and females 18 years of age or older
- Skin and skin structure infection that either:
  - Involved deeper soft tissue and/or required significant surgical intervention such as a wound infection (surgical or traumatic), a major abscess, an infected ulcer, or deep and extensive cellulitis; or
  - Lower extremity cSSTI that occurred in a subject with diabetes mellitus (DM) or well-documented peripheral vascular disease (PVD)
- Clinical findings from both of the following categories:
  - Local signs at the cSSTI site (at least two): purulent or seropurulent drainage or discharge; erythema; fluctuance; heat or localized warmth; pain or tenderness to palpation; or swelling or induration
  - Systemic signs (at least one): fever greater than 38°C orally; white blood cell (WBC) count greater than 10,000/mm^3; C. Greater than 10% immature neutrophils (bands), irrespective of WBC count
- The subject's infection and/or condition, by the standard of care, required at least initial hospitalization
- The subject's infection, by the standard of care, required treatment with IV Antimicrobials

The exclusion criteria included:

- History of any hypersensitivity or allergic reaction to any ß-lactam antibiotic, any sulphite or vancomycin
- Past or current history of epilepsy or seizure disorder
- More than a single dose of a non-study antimicrobial, including topical therapy, for treatment of the current cSSTI within the 96 hr leading up to randomisation
- Pre-existing Gram-positive infection known or suspected to be resistant to vancomycin, or Gram-negative infection known or suspected to be resistant to aztreonam or ceftriaxone

- Furunculosis, carbunculosis, or folliculitis
- Skin and skin structure infection with:
  - Known or suspected anaerobic pathogens, fungal, parasitic, or viral pathogens
  - Known or suspected Pseudomonas aeruginosa as a contributing pathogen
  - Involving an ischemic ulcer due to PVD; a decubitus ulcer or a diabetic foot ulcer
  - Involving a third-degree burn or a burn covering more than 5% of total body surface area
  - Involving an underlying inflammatory skin disease that may obscure determination of response, such as atopic dermatitis where inflammation may be prominent for an extended period of time, even after successful bacterial eradication has been achieved
  - Involving a bite other than an arthropod bite (i.e. no human or animal bites)
  - Involving a rapidly necrotizing process, such as necrotizing fasciitis
  - Involving gangrene of any etiology
  - Complicated by an immune deficiency in the subject (for example, development of ecthyma gangrenosum in neutropenic subjects)
  - Complicated by the presence of prosthetic materials that were not to be removed, such as central venous catheters, permanent cardiac pacemaker battery packs, or joint replacement prostheses
  - Requiring amputation
  - Requiring significant surgical intervention that cannot be performed within 48 hr after initiating study drug therapy
- Skin and skin structure infections with a high cure rate after surgical incision alone or after aggressive local skin care
- Skin and skin structure infections of the same type at separate and distinct anatomic sites, such as multiple skin abscesses
- Known or suspected infections related to the cSSTI but present at or originating from other anatomic sites or spaces, such as endocarditis, osteomyelitis, or septic arthritis
- Requirement for concomitant antibacterial or systemic antifungal therapy for any reason
- Requirement for concomitant therapy with valproic acid or probenecid
- Probenecid administration within 3 days prior to initiation of study drug
- Requirement for concomitant therapy with anti-arrhythmic agents Class Ia or Class III which are known to prolong markedly the QTc
- Infections or conditions requiring concomitant systemic corticosteroids
- Moderately or severely impaired renal function defined as creatinine clearance (CrCl) <50 mL/min estimated by the Cockroft-Gault formula
- Evidence of significant hepatic, hematologic, or immunologic disease
- Evidence of immediate life-threatening disease
- Evidence of significant cardiac disease
- History of nephrolithiasis
- Life expectancy of <3 months

- Women who were pregnant, nursing, or of childbearing potential not using an acceptable method of birth control

6.1.1.1.3. Study treatments

The study treatments were:

1. ceftaroline 600 mg, IV over 60 minutes, q12h
2. vancomycin 1 g, IV, q12h. When a culture indicated a PRP-susceptible Gram-positive organism (for example, S. pyogenes or MSSA), the Investigator had the option to change therapy from vancomycin to a PRP (nafcillin, oxacillin, flucloxacillin, or cloxacillin) if the change was performed within the first 72 hr after initiation of study drug therapy. All subjects randomised to the comparator group could receive aztreonam (1 g), IV, infused over 30 minutes q8h as concomitant empiric therapy if the baseline clinical presentation, the Gram's stain of the cSSTI site specimen and/or the culture results from the cSSTI site or blood specimen indicated infection with a Gram-negative organism. Once started, aztreonam could be discontinued at any time at the discretion of the Investigator. Vancomycin, nafcillin, oxacillin, flucloxacillin, cloxacillin and aztreonam were to be prepared and administered according to local product information specifications.

Treatment duration was for 7 to 14 days, depending upon response.

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was clinical response at TOC visit, 8 to 14 days post therapy. Secondary efficacy outcome measures were:

- Clinical response at EOT visit
- Microbiological response at TOC
- Clinical and microbiological response at TOC in the subgroup with MRSA
- Relapse at LFU visit
- Reinfection or recurrence at LFU

The safety outcome measures were: AEs, clinical laboratory tests and ECGs. Blood samples were also collected for pharmacokinetic analysis at selected sites.

The clinical response categories were defined as:

- Clinical Cure: Total resolution of all signs and symptoms of the cSSTI, or improvement to such an extent that further antimicrobial therapy is not necessary. For diabetic subjects with an underlying skin ulcer, healing of the ulcer was not required for an outcome of cure
- Clinical Failure:
  - Persistence, incomplete resolution, or worsening in signs and symptoms of the cSSTI that requires further antimicrobial therapy
  - An unplanned surgical intervention that was performed as an adjunct or follow-up therapy due to failure of the study drug to adequately treat the infection
  - New signs and symptoms associated with the original cSSTI or a new cSSTI at the same anatomical site
  - Subject required additional antibiotic therapy to treat the cSSTI, including oral step-down therapy
  - For subjects receiving vancomycin whose baseline isolate is a methicillin-susceptible pathogen, a switch to a PRP >72 hr after initiation of study drug therapy

  - Death wherein cSSTI is considered causative

- Indeterminate: Study data were not available for evaluation of efficacy for any reason, including treatment change prior to completing at least 48 hr of study drug therapy; death wherein cSSTI is clearly non-contributory, loss to follow-up, or extenuating circumstances preclude classification as a cure or failure

The microbiological response categories were defined as:

- Eradication: An adequate source specimen demonstrates absence of the original baseline pathogen
- Presumed Eradication: No adequate source specimen to culture and the subject was assessed as a clinical cure.
- Persistence: Source specimen demonstrates continued presence of the original baseline pathogen.
- Presumed Persistence: No adequate source specimen to culture and the subject was assessed as a clinical failure.
- Indeterminate: No adequate source specimen to culture and the subject's clinical response was assessed as indeterminate.

Additional microbiological response categories were: superinfection, colonisation and recurrence/reinfection.

The Test of Cure (TOC) assessment was performed 8 to 14 days after End of Treatment (EOT). The Late Follow-Up (LFU) assessment occurred 21 to 28 days after EOT. The schedule of study visits was indicated in the study report.

6.1.1.1.5. Randomisation and blinding methods

Randomisation occurred after baseline assessment. Randomisation was 2:1, ceftaroline: standard treatment, using a computer generated randomisation schedule and IVRS. The study was single blinded.

6.1.1.1.6. Sample size

The study was not powered to test any hypothesis but was designed as a Phase II study in order to test proof of concept. With a sample size of 100 subjects, assuming a dropout rate of 20% and a response rate of 80% in each treatment group, 54 subjects in the test group and 26 in the comparator would yield a 95% CI of 69.3% to 90.7% and 64.6% to 95.4% respectively.

6.1.1.1.7. Statistical methods

Formal hypothesis tests were not performed. Response rate and their 95% CI were determined for each group separately.

6.1.1.1.8. Participant flow

There were 67 subjects randomised to ceftaroline and 33 to comparator. One subject in the comparator group did not receive treatment. There were 59 (88.1%) subjects in the ceftaroline group and 26 (78.8%) in the comparator that completed the study[21]. The reasons for exclusion from the CE population were summarised in the study report.

[21] Sponsor clarification: "These numbers related to those who completed the study drug, not those who completed the study."

6.1.1.1.9. Baseline data

In the treated population (cMITT) there were 56 (56.6%) males, 43 (43.4%) females and the age range was 18 to 84 years. The treatment groups were similar in past medical history. The infections were primarily abscess and cellulitis with primarily limb involvement. Microbiological characteristics were similar for the two treatment groups. Staphylococcal, particularly MRSA, isolates were more common in the comparator group. There was no apparent difference in the pattern of Gram negative isolates. Bacteraemia at baseline was more common in the comparator group: four (14.8%) subjects compared with two (3.9%) in the ceftaroline. There were four isolates with MIC >1 µg/mL, all of which were Gram negative. In the cMITT Population, 36 (53.7%) of subjects in the ceftaroline group and 16 (50.0%) in the comparator group received antimicrobials within 4 weeks prior to randomisation. Duration of treatment was, median (range), 6.7 (0.4 to 19.5) days in the ceftaroline group and 7.4 (2.0 to 20.5) in the comparator.

6.1.1.1.10. Results for the primary efficacy outcome

For the primary efficacy outcome variable, in the cMITT population, the cure rate (95% CI) was 88.1% (77.8% to 94.7%) in the ceftaroline population and 81.3% (63.6% to 92.8%) in the comparator (Table 8).

Table 8. Clinical Response at Test-of-Cure Visit by Clinically Evaluable and Clinical Modified Intent-to-Treat Populations

Investigator Response	n (%) CE (95% CI)		n (%) cMITT (95% CI)	
	PPI-0903 N=61	Comparator N=27	PPI-0903 N=67	Comparator N=32
Cure	59 (96.7) (88.7%-99.6%)	24 (88.9) (70.8%-97.6%)	59 (88.1) (77.8%-94.7%)	26 (81.3) (63.6%-92.8%)
Failure	2 (3.3)	3 (11.1)	2 (3.0)	3 (9.4)
Indeterminate[1]	NA	NA	6 (9.0)	3 (9.4)

Abbreviations: CI=Confidence interval; CE=Clinically Evaluable; cMITT=Clinical Modified Intent-to-Treat; NA=Not applicable.

1. By definition, responses in the CE Population cannot be indeterminate.

6.1.1.1.11. Results for other efficacy outcomes

At EOT visit the cure rate (95% CI) was 91.0% (81.5% to 96.6%) in the ceftaroline group and 87.5% (71.0% to 96.5%) in the comparator. Microbiological eradication at TOC occurred in 84.3% (71.4% to 93.0%) subjects in the ceftaroline group and 77.8% (57.7% to 91.4%) in the comparator. There were six subjects with MRSA at baseline in each group and cure was recorded for four (66.7%) in the ceftaroline group and five (83.3%) in the comparator. At LFU relapse was recorded of one (1.8%) subjects in the ceftaroline group and one (4.2%) in the comparator. There were no re-infections at LFU. Decreasing susceptibility (a 4-fold increase in MIC from the baseline value at a subsequent time point) to ceftaroline during treatment was not documented in any isolate.

6.1.1.2. 6.1.1.2 Study P903-06

6.1.1.2.1. Study design, objectives, locations and dates

Study P903-06 was a multicentre, randomised, double blind, comparator controlled, parallel group, Phase III, non-inferiority, efficacy and safety study of ceftaroline fosamil compared to vancomycin plus aztreonam in adult subjects with cSSTI. The study was sponsored by Cerexa, Inc and conducted in Eastern Europe, Latin America, the US and Western Europe from February to November 2007.

6.1.1.2.2. Inclusion and exclusion criteria

The inclusion criteria were similar to Study P903-03 with the main difference being that subjects had to require at least 5 days of IV antimicrobial therapy. The exclusion criteria were essentially the same as for Study P903-03.

6.1.1.2.3. Study treatments

The study treatments were:

1. Ceftaroline fosamil 600 mg, intravenous over 60 minutes, q12h (dose modified to 400 mg in moderate renal failure) and placebo q12h
2. Vancomycin 1 g, intravenous over 60 minutes, q12h (dose modified according to local guidelines in moderate renal failure but either q12h or q24h with additional placebo to maintain blinding) and aztreonam 1 g, intravenous over 60 minutes, q12h

Treatment duration was for 5 to 7 days.

6.1.1.2.4. Efficacy variables and outcomes

The primary efficacy outcome measure was clinical cure at TOC visit in the CE and cMITT[22] populations. The secondary efficacy outcome measures were the same as for Study P903-03 with the addition of:

- Clinical response at TOC visit

The safety outcome measures were the same as for Study P903-03. The schedule of study visits was shown in the study report.

The criteria for treatment failure also included:

- Treatment-limiting AE leading to study drug discontinuation, when subject required alternative antimicrobial therapy to treat the cSSTI, including oral step-down therapy
- Diagnosis of osteomyelitis 8 or more days after randomisation.

6.1.1.2.5. Randomisation and blinding methods

Randomisation was 1:1 by computer generated block randomisation with stratification by country, using IVRS. Blinding was maintained using placebo to maintain an equivalent number and timing of intravenous injections.

6.1.1.2.6. Analysis populations

The ITT population consisted of all randomised subjects. The MITT population consisted of all randomised subjects who received any amount of study drug. The cMITT population consisted of all subjects in the MITT population who met the minimal disease criteria for a cSSTI. The mMITT population consisted of all subjects in the cMITT Population who had at least one bacterial pathogen identified from a blood culture or from a culture of an adequate microbiological sample obtained from the cSSTI site at baseline.

6.1.1.2.7. Sample size

The sample size estimation was based on a non-inferiority comparison. A 10% non-inferiority margin was considered to preserve at least 50% of the effect size of vancomycin. The Sponsor discussed the margin for non-inferiority with the FDA. Based on recent registration studies, the clinical cure rate for vancomycin was taken to be 88%, with a 95% CI lower limit of 83.2%. The upper 95% CI for the putative placebo effect was 61.5%. Half the difference between the lower

[22] Erratum: MITT population not cMITT

95% CI for vancomycin and the upper 95% CI for placebo was 10.9%. Hence 10.9% was taken to be the upper limit for a non-inferiority margin to preserve 50% of the effect of vancomycin.

6.1.1.2.8. Statistical methods

Hypothesis tests were performed using 95% CI for the difference in event rates.

6.1.1.2.9. Participant flow

A total of 702 subjects were randomised to treatment: 353 to ceftaroline and 349 to comparator. In the cMITT population there were 345 subjects in the ceftaroline group and 344 in the comparator. In the mMITT population there were 271 subjects in the ceftaroline group and 263 in the comparator. The analysis populations are summarised in Figure 7.1.1.2.1. There were 325 (92.1%) subjects in the ceftaroline group and 315 (90.3%) in the comparator that completed the study[23]. The reasons for discontinuation are summarised in Table 9.

[23] Sponsor clarification: "These numbers related to those who completed the study drug, not those who completed the study."

Table 9. Premature Discontinuations from Study Drug Therapy and Withdrawals from the Study (ITT Population)

Subject Status and Reasons for Discontinuation	*Ceftaroline (N = 353) n (%)*	*Vancomycin plus Aztreonam (N = 349) n (%)*	*Total (N = 702) n (%)*
Completed study drug	325 (92.1)	315 (90.3)	640 (91.2)
Prematurely discontinued from study drug	28 (7.9)	34 (9.7)	62 (8.8)
Reason for premature discontinuation of study drug			
Adverse event[a]	13 (3.7)	15 (4.3)	28 (4.0)
Lost to follow-up	4 (1.1)	7 (2.0)	11 (1.6)
Insufficient therapeutic effect	3 (0.8)	5 (1.4)	8 (1.1)
Significant surgical intervention	2 (0.6)	0	2 (0.3)
Resistant pathogen	1 (0.3)	2 (0.6)	3 (0.4)
Lack of clinical progress	0	2 (0.6)	2 (0.3)
Clinical worsening	0	1 (0.3)	1 (0.1)
Did not receive study drug	1 (0.3)	2 (0.6)	3 (0.4)
Concomitant antimicrobial therapy	1 (0.3)	1 (0.3)	2 (0.3)
Met exclusion criteria	1 (0.3)	1 (0.3)	2 (0.3)
Incarceration	1 (0.3)	0	1 (0.1)
Other	4 (1.1)	3 (0.9)	7 (1.0)
Completed study	329 (93.2)	317 (90.8)	646 (92.0)
Withdrew from study	24 (6.8)	32 (9.2)	56 (8.0)
Reason for withdrawal from the study			
Lost to follow-up	14 (4.0)	19 (5.4)	33 (4.7)
Withdrew consent	3 (0.8)	4 (1.1)	7 (1.0)
Death	3 (0.8)	0	3 (0.4)
Randomized, but did not receive study drug	2 (0.6)	2 (0.6)	4 (0.6)
Noncompliance	1 (0.3)	2 (0.6)	3 (0.4)
Incarceration	1 (0.3)	0	1 (0.1)
Request of Sponsor or Investigator	0	2 (0.6)	2 (0.3)
Diagnosis of osteomyelitis	0	1 (0.3)	1 (0.1)
Met exclusion criteria	0	1 (0.3)	1 (0.1)
Other	0	1 (0.3)	1 (0.1)

Abbreviations: ITT = intent-to-treat.

a Subject 0002-06061 in the vancomycin plus aztreonam group discontinued outpatient study drug therapy prematurely due to insufficient therapeutic effect. The subject was hospitalized to receive IV antibiotic therapy and thus, an SAE of wound infection was reported. The subject appears on this table as a discontinuation due to insufficient therapeutic effect. and on Table 12.3.3.1-1, Table 14.5.2.5, and Table 14.5.2.6 as a premature discontinuation of study drug due to a wound infection.

6.1.1.2.10. Baseline data

In the MITT population there were 438 (62.8%) males, 260 (37.2%) females and the age range was 18 to 90 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in past medical history. The clinical characteristic of the infection were similar for the two treatment groups. The infection sites were of similar mean size. The types of infection were similarly distributed for the two treatment groups. The infections were sited primarily on the limbs. The infections were predominantly Staphylococcal, with around 30% being MRSA. Other than the Enterococcus faecalis isolates, the Gram positive isolates were susceptible to ceftaroline but the Gram negative organisms were predominantly not

susceptible.[24] Disease severity at baseline was similar for the two groups. Additional systemic antibacterial treatment[25] was required by 25 (7.1%) subjects in the ceftaroline group and 26 (7.5%) in the comparator.

6.1.1.2.11. Results for the primary efficacy outcome

For the primary efficacy outcome measure, non-inferiority was demonstrated by the predefined non-inferiority criteria. For the CE population, clinical cure was recorded for 288 (91.1%) subjects in the ceftaroline group and 280 (93.3%) subjects in the comparator, difference (95% CI) -2.2% (-6.6% to 2.1%) (Table 10). For the MITT population, clinical cure was recorded for 304 (86.6%) subjects in the ceftaroline group and 297 (85.6%) in the comparator, difference (95% CI) 1.0% (-4.2% to 6.2%). Clinical cure rates were worse for ceftaroline in Chile, Peru and Poland; and better in the US.[26] Clinical cure rates were also worse for subjects >75 years age: 15 (78.9%) of 19 in the ceftaroline group compared to 20 (90.9%) of 22 in the comparator, difference (95% CI) -12.0% (-6.4% to 11.0%) (Table 11).

Table 10. Clinical Response at the Test-of-cure Visit—Noninferiority and Superiority Tests (CE and MITT Populations)

Population	*Clinical Response*	*Ceftaroline n (%)*	*Vancomycin plus Aztreonam n (%)*	*Difference[a] (95% CI[b])*	*p-value[c] for Superiority*
CE, N		316	300		
	Clinical cure	288 (91.1)	280 (93.3)	-2.2 (-6.6, 2.1)	p = .367
	Clinical failure	28 (8.9)	20 (6.7)		
MITT, N		351	347		
	Clinical cure	304 (86.6)	297 (85.6)	1.0 (-4.2, 6.2)	p = .743
	Clinical failure	29 (8.3)	21 (6.1)		
	Indeterminate	18 (5.1)	29 (8.4)		

Abbreviations: CE = clinically evaluable; CI = confidence interval; MITT = modified intent-to-treat.

a Difference = ceftaroline group minus vancomycin plus aztreonam group.

b CIs are calculated using the Miettinen and Nurminen method without adjustment.

c p-values are calculated using Fisher's Exact Test.

[24] Sponsor clarification: "In the pooled ME population the majority of Gram-negative organisms were susceptible to ceftaroline with the exception of *Pseudomonas aeroginosa* (see PI "Pharmacology/Susceptibility testing" section) and *Proteus mirabilis*."

[25] Sponsor clarification: "antibacterial treatment *before TOC* was required by 25 (7.1%) subjects in the ceftaroline group and 26 (7.5%) in the comparator."

[26] Sponsor clarification: "In many cases the number of patients recruited in individual countries was small."

Table 11.Clinical Cure at the TOC Visit by Subgroups (CE Population)

Subgroup	*Ceftaroline n[b]/N[a] (%)*	*Vancomycin plus Aztreonam n[b]/N[a] (%)*	*Difference[c] (95% CI)[d]*
Subjects with ≥ 2 severe signs and symptoms at baseline	164/176 (93.2)	164/176 (93.2)	0.0 (-5.6 , 5.6)
Subjects with fever	105/111 (94.6)	97/101 (96.0)	-1.4 (-7.9, 5.0)
Subjects without fever	183/204 (89.7)	183/199 (92.0)	-2.3 (-8.1, 3.5)
Subjects with elevated WBC count (> 10^3/mm^3)	93/106 (87.7)	97/104 (93.3)	-5.5 (-14.4, 2.6)
Subjects without elevated WBC count (≤ 10,000/mm^3)	162/175 (92.6)	153/165 (92.7)	-0.2 (-6.0, 5.7)
Subjects with ≥ 2 severe signs and symptoms, fever, or elevated WBC count (> 10,000/mm^3)	216/238 (90.8)	205/220 (93.2)	-2.4 (-7.6, 2.7)
Subjects > 75 years of age	15/19 (78.9)	20/22 (90.9)	-12.0 (-36.4, 11.0)
Subjects ≤ 75 years of age	273/297 (91.9)	260/278 (93.5)	-1.6 (-6.0, 2.8)
Subjects with diabetes mellitus	49/56 (87.5)	57/61 (93.4)	-5.9 (-18.1, 5.1)
Subjects with PVD	41/45 (91.1)	41/45 (91.1)	0.0 (-13.3, 13.3)
Subjects with monomicrobial infection	161/179 (89.9)	142/152 (93.4)	-3.5 (-9.6, 2.8)
Subjects with polymicrobial infection	62/65 (95.4)	76/79 (96.2)	-0.8 (-9.4, 6.7)
Subjects with monomicrobial MRSA	62/66 (93.9)	40/43 (93.0)	0.9 (-8.9, 13.3)
Subjects with polymicrobial MRSA	14/14 (100.0)	18/18 (100.0)	0.0 (-22.1, 18.1)
Subjects with moderate renal dysfunction (30 < CrCl ≤ 50)	10/12 (83.3)	11/13 (84.6)	-1.3 (-33.6, 30.1)
Subjects with normal renal function or mild renal impairment (CrCl > 50)	277/303 (91.4)	268/286 (93.7)	-2.3 (-6.7, 2.1)
Subjects with at least 1 systemic sign	163/179 (91.1)	158/167 (94.6)	-3.5 (-9.3, 2.1)
Subjects with abscess, at least 1 dimension > 5 cm	65/74 (87.8)	64/67 (95.5)	-7.7 (-17.8, 1.8)

Abbreviations: CE = clinically evaluable; CI = confidence interval; CrCl = creatinine clearance; MRSA = methicillin-resistant *S. aureus*; PVD = peripheral vascular disease; WBC = white blood cell.

a N = Number of subjects with the specified pathogen in the ME Population at baseline.
b n = Number of subjects clinically cured.
c Difference = ceftaroline group minus vancomycin plus aztreonam group.
d CIs are calculated using the Miettinen and Nurminen method without adjustment.

6.1.1.2.12. Results for other efficacy outcomes

For the MITT[27] population, a favourable microbiological response at TOC was recorded for 234 (86.3%) subjects in the ceftaroline group and 220 (83.7%) in the comparator, difference (95% CI) 2.7% (-3.4% to 8.9). Clinical cure at EOT visit[28] was recorded for 322 (91.7%) subjects in the ceftaroline group and 313 (90.2%) in the comparator, difference (95% CI) 1.5% (-2.8% to 5.9%). Clinical response by baseline pathogen[29] was similar for the two treatment groups for Gram positive organisms but there was a poorer response in the ceftaroline group for Gram

[27] Sponsor erratum: mMITT population not MITT population"
[28] Sponsor clarification: "in the MITT population"
[29] Sponsor clarification: "in the ME population"

negative organisms. Three subjects in each treatment group experienced a clinical relapse at LFU after having been assessed as cured at TOC.

6.1.1.3. Study P903-07

6.1.1.3.1. Study design, objectives, locations and dates

Study P903-07 was a multicentre, randomised, double blind, comparator controlled, parallel group, Phase III, non-inferiority, efficacy and safety study of ceftaroline fosamil compared to vancomycin plus aztreonam in adult subjects with cSSTI. The study was sponsored by Cerexa, Inc and conducted in 56 study centres in twelve countries (13 centres in Eastern Europe, 14 in Latin America, 15 in the US and 14 in Western Europe) from March 2007 to December 2007. The study was identical in design to Study P903-06.

6.1.1.3.2. Participant flow

A total of 694 subjects were randomised to treatment: 348 to ceftaroline and 346 to comparator. In the CE population there were 294 (84.5%) subjects in the ceftaroline group and 292 (84.4%) in the comparator. In the cMITT population there were 341 (98.0%) subjects in the ceftaroline group and 337 (97.4%) in the comparator. In the mMITT population there were 269 (77.3%) subjects in the ceftaroline group and 259 (74.9%) in the comparator. The primary reason for exclusion from the CE population was indeterminate cure at the TOC visit. A total of 316 (90.8%) subjects in the ceftaroline group and 313 (90.5%) in the comparator completed the study. The pattern of reasons of withdrawal was similar for the two treatment groups.

6.1.1.3.3. Baseline data

There were 425 (62.5%) males, 255 (37.5%) females and the age range was 18 to 96 years. There was a 6% male/female disparity, with 6% more males in the ceftaroline group but other than this the treatment groups were similar in demographic characteristics. The treatment groups were similar in past medical history. The treatment groups were similar in signs and symptoms of cSSTI at baseline. Lesion size was similar for the two treatment groups. The treatment groups were similar in type and site of infection. Around 80% of the isolated pathogens were Staphylococcus aureus with 30% being MRSA. The distribution of pathogens was similar for the two treatment groups. The Gram positive organisms were susceptible to ceftaroline and vancomycin but the Gram negative organisms, with the exception of Escherichia coli were not susceptible to ceftaroline.[30] Disease severity was similar at baseline. Prior antibiotics in the 96 hr prior to randomisation were received by 119 (34.8%) subjects in the ceftaroline group and 110 (32.5%) in the comparator. Addition systemic antibiotic treatments were received, from randomisation to TOC, by 30 (8.8%) subjects in the ceftaroline group and 30 (8.9%) in the comparator.

6.1.1.3.4. Results for the primary efficacy outcome

For the primary efficacy outcome measure, non-inferiority was demonstrated by the predefined non-inferiority criteria. For the CE population, clinical cure was recorded for 271 (92.2%) subjects in the ceftaroline group and 269 (92.1%) subjects in the comparator, difference (95% CI) 0.1% (-4.4% to 4.5%) (Table 12). For the MITT population, clinical cure was recorded for 291 (85.1%) subjects in the ceftaroline group and 289 (85.5%) in the comparator, difference (95% CI) -0.4% (-5.8% to 5.0%). Clinical cure rates were worse for ceftaroline in Latvia and Argentina; and better in Brazil, Mexico and Germany[31]. Clinical cure rates were also slightly better for subjects >75 years age: 20 (83.3%) of 24 in the ceftaroline group compared to 15 (78.9%) of 19 in the comparator, difference (95% CI) 4.4% (-19.5% to 30.0%) (Table 13).

[30] Sponsor clarification: "In the pooled ME population the majority of Gram-negative organisms were susceptible to ceftaroline with the exception of *Pseudomonas aeroginosa* (see PI "Pharmacology/Susceptibility testing" section) and *Proteus mirabilis*."
[31] Sponsor clarification: "In many cases the number of patients recruited in individual countries was small."

Table 12. Disease Severity at Baseline (MITT Population)

Disease Severity	*Ceftaroline (N = 342)*	*Vancomycin plus Aztreonam (N = 338)*	*Total (N = 680)*
Medical history, n (%)			
Subjects > 75 years of age	24 (7.0)	19 (5.6)	43 (6.3)
Subjects with diabetes	60 (17.5)	52 (15.4)	112 (16.5)
Subjects with PVD	46 (13.5)	40 (11.8)	86 (12.6)
Subjects with moderate renal dysfunction ($30 < CrCl \leq 50$)	13 (3.8)	13 (3.8)	26 (3.8)
Prior failures[a]	31 (9.1)	26 (7.7)	57 (8.4)
Signs and symptoms, n (%)			
Subjects with temperature available	342	338	680
Subjects with fever	90/342 (26.3)	91/338 (26.9)	181/680 (26.6)
Subjects with WBC count available	306	305	611
Subjects with elevated WBC count ($> 10^3/mm^3$)	126/306 (41.2)	127/305 (41.6)	253/611 (41.4)
Subjects with at least 1 systemic sign[b]	179 (52.3)	169 (50.0)	348 (51.2)
Subjects with 2 or more signs or symptoms classified as severe[c]	181 (52.9)	176 (52.1)	357 (52.5)
Subjects with 2 or more signs and symptoms classified as severe[c], fever, or elevated WBC count ($> 10^3/mm^3$)	245 (71.6)	234 (69.2)	479 (70.4)
Other signs and symptoms			
Subjects with bacteremia, n (%)	9 (2.6)	14 (4.1)	23 (3.4)
Subjects with abscess with at least one dimension > 5 cm, n (%)[d]	124/139 (89.2)	120/133 (90.2)	244/272 (89.7)
Infection area (cm^2), median (range)	151.0 (1.4, 2860.0)	120.0 (0, 4950.0)	136.0 (0, 4950.0)

Abbreviations: CrCl = creatinine clearance; MITT = modified intent-to-treat; PVD = peripheral vascular disease; WBC = white blood cell.

a Subjects who received > 48 hours of systemic antibiotic therapy with evidence of prior failure (positive Gram's stain or isolation of resistant organism) before administration of study drug.

b Fever greater than 38°C oral (> 38.5°C rectally or tympanically) or hypothermia (< 35°C), WBC count greater than $10,000/mm^3$, greater than 10% immature neutrophils (bands) irrespective of WBC count.

c Erythema, swelling, tenderness, or warmth.

d Denominator is the number of subjects with major abscess.

Table 13. Clinical Response at the Test-of-cure Visit by Subgroups (MITT Population)

Subgroup	Clinical Response	Ceftaroline n (%)	Vancomycin plus Aztreonam n (%)	Difference	95% CI for the Difference
Subjects with 2+ Signs and Symptoms at Baseline of Severe	N	181	176		
	Clinical Cure	161 (89.0)	159 (90.3)	-1.4	(-7.9, 5.1)
	Clinical Failure	12 (6.6)	10 (5.7)		
	Indeterminate	8 (4.4)	7 (4.0)		
Subjects with Fever	N	90	91		
	Clinical Cure	76 (84.4)	82 (90.1)	-5.7	(-15.9, 4.3)
	Clinical Failure	8 (8.9)	4 (4.4)		
	Indeterminate	6 (6.7)	5 (5.5)		
Subjects without Fever	N	252	247		
	Clinical Cure	215 (85.3)	207 (83.8)	1.5	(-4.9, 7.9)
	Clinical Failure	17 (6.7)	24 (9.7)		
	Indeterminate	20 (7.9)	16 (6.5)		
Subjects with Elevated WBC Count (>10,000 cells/mm^3)	N	126	127		
	Clinical Cure	108 (85.7)	108 (85.0)	0.7	(-8.2, 9.6)
	Clinical Failure	11 (8.7)	11 (8.7)		
	Indeterminate	7 (5.6)	8 (6.3)		
Subjects without Elevated WBC Count (<=10,000 cells/mm^3)	N	180	178		
	Clinical Cure	153 (85.0)	151 (84.8)	0.2	(-7.4, 7.7)
	Clinical Failure	10 (5.6)	15 (8.4)		
	Indeterminate	17 (9.4)	12 (6.7)		
Subjects with 2+ Signs and Symptoms at Baseline of Severe, Fever, or Elevated WBC Count (>10,000 cells/mm^3)	N	245	234		
	Clinical Cure	213 (86.9)	205 (87.6)	-0.7	(-6.7, 5.4)
	Clinical Failure	17 (6.9)	16 (6.8)		
	Indeterminate	15 (6.1)	13 (5.6)		
Subjects Age >75 Years	N	24	19		
	Clinical Cure	20 (83.3)	15 (78.9)	4.4	(-19.5, 30.0)
	Clinical Failure	2 (8.3)	3 (15.8)		
	Indeterminate	2 (8.3)	1 (5.3)		
Subjects Age <=75 Years	N	318	319		
	Clinical Cure	271 (85.2)	274 (85.9)	-0.7	(-6.2, 4.8)
	Clinical Failure	23 (7.2)	25 (7.8)		
	Indeterminate	24 (7.5)	20 (6.3)		
Subjects with DM	N	60	52		
	Clinical Cure	50 (83.3)	45 (86.5)	-3.2	(-16.8, 10.9)
	Clinical Failure	7 (11.7)	7 (13.5)		
	Indeterminate	3 (5.0)	0		
Subjects with PVD	N	46	40		
	Clinical Cure	39 (84.8)	35 (87.5)	-2.7	(-18.0, 13.2)
	Clinical Failure	7 (15.2)	5 (12.5)		
	Indeterminate	0	0		
Subjects with Monomicrobial Infection	N	190	191		
	Clinical Cure	168 (88.4)	166 (86.9)	1.5	(-5.2, 8.3)
	Clinical Failure	9 (4.7)	13 (6.8)		
	Indeterminate	13 (6.8)	12 (6.3)		
Subjects with Polymicrobial Infection	N	79	67		
	Clinical Cure	66 (83.5)	59 (88.1)	-4.5	(-16.1, 7.4)
	Clinical Failure	8 (10.1)	3 (4.5)		
	Indeterminate	5 (6.3)	5 (7.5)		

6.1.1.3.5. Results for other efficacy outcomes

For the MITT population[32], a favourable microbiological response at TOC was recorded for 233 (86.6%) subjects in the ceftaroline group and 229 (88.4%) in the comparator, difference (95% CI) -1.8% (-7.5% to 3.9%). Clinical cure at EOT visit[33] was recorded for 304 (88.9%) subjects in the ceftaroline group and 302 (89.3%) in the comparator, difference (95% CI) -0.5% (-5.2% to 4.3%). Clinical response by baseline pathogen was similar for the two treatment groups for Gram positive organisms but there was a poorer response in the ceftaroline group for Gram negative organisms. Three subjects in the ceftaroline group and two in the comparator experienced a clinical relapse at LFU after having been assessed as cured at TOC.

[32] Sponsor erratum: mMITT population not MITT population
[33] Sponsor clarification: "in the MITT population"

6.1.1.4. Study P903-19

6.1.1.4.1. Study design, objectives, locations and dates

Study P903-19 was a multicentre, randomised, open-label, parallel group, comparator controlled (linezolid), Phase II study of intramuscular ceftaroline in adults with cSSTI. The study was sponsored by Cerexa, Inc and conducted at 12 centres in the US from February 2008 to July 2008.

6.1.1.4.2. Inclusion and exclusion criteria

The inclusion criteria were the same as for Study P903-03 with the exception of the replacement of:

- The subject's infection, by the standard of care, required treatment with IV antimicrobials

With

- The subject was expected to be able to tolerate multiple IM injections for the expected duration of study drug administration

The exclusion criteria were similar to those for Study P903-03 with the addition of allergic and hypersensitivity reactions to linezolid.

6.1.1.4.3. Study treatments

The study treatments were:

1. Ceftaroline fosamil 600 mg IM, q12h
2. Linezolid 600 mg IV infusions over 60 minutes q12h. Aztreonam may have been started with linezolid or up to 72 hr after the first dose of linezolid if a mixed Gram-positive and Gram-negative infection been indicated or suspected at baseline.

Treatment duration was for 5 to 14 days. Randomisation to treatment group was in the ratio of 2:1, ceftaroline to comparator. The study was open-label.

6.1.1.4.4. Efficacy variables and outcomes

The clinical response categories differed from Study P903-03 by the inclusion of the following additional criteria for treatment failure:

- Treatment-limiting AE leading to study drug discontinuation, when subject required alternative antimicrobial therapy to treat the cSSTI, including oral step-down therapy
- Diagnosis of osteomyelitis 8 or more days after randomisation

The schedule of study visits was summarised in the study report.

6.1.1.4.5. Sample size

The study was not powered for hypothesis tests. Assuming an 85% clinical cure rate in the ceftaroline group, a sample size of 80 subjects would yield a 95% CI around the clinical cure rate of 77.5% to 92.5%. Assuming an 85% clinical cure rate in the linezolid group, a sample size of 40 subjects would yield a 95% CI around the clinical rate of 74.0% to 96.0%.

6.1.1.4.6. Participant flow

A total of 150 subjects were randomised to treatment: 103 to ceftaroline and 47 to comparator. The MITT population included 98 (95.1%) subjects in the ceftaroline group and 45 (95.7%) in the comparator. The cMITT population included 97 (94.2%) subjects in the ceftaroline group and 44 (93.6%) in the comparator. The mMITT population included 77 (74.8%) subjects in the ceftaroline group and 38 (80.9%) in the comparator. The CE population included 86 (83.5%)

subjects in the ceftaroline group and 39 (83.0%) in the comparator. A total of 86 (83.5%) subjects in the ceftaroline group and 42 (89.4%) in the comparator completed the study[34].

6.1.1.4.7. Baseline data

There were 96 (67.1%) males, 47 (32.9%) females and the age range was 18 to 89 years. The treatment groups were similar in demographic and baseline characteristics. A lower proportion of subjects in the ceftaroline group had recent trauma and a higher proportion had diabetes mellitus. The treatment groups were similar in clinical features. The lesions were similar in location and descriptive features. A high proportion of the isolates were MRSA, with a slightly higher proportion in the ceftaroline group: 47 (61.0%) isolates compared with 21 (55.3%) in the comparator. The treatment groups were similar in clinical severity. Thirty nine (39.8%) subjects in the ceftaroline group and 18 (40.0%) in the comparator had received systemic antibiotics in the 96 hr prior to randomisation. Six (6.1%) subjects in the ceftaroline group and one (2.2%) in the comparator received additional systemic antibacterial treatment from randomisation through to TOC. The MIC range for the MRSA was higher for linezolid than for ceftaroline: 1 to 2 µg/ml compared to 0.25 to 1 µg/mL respectively.

6.1.1.4.8. Results for the primary efficacy outcome

For the MITT population, the clinical cure rate (95% CI) at TOC was 84.7% (76.0% to 91.2%) for ceftaroline and 88.9% (75.9% to 96.3%) for comparator (Table 7.1.1.4.11). There were too few subjects to enable subgroup comparisons.

6.1.1.4.9. Results for other efficacy outcomes

For the cMITT population, the clinical cure rate (95% CI) at TOC was 84.5% (75.8% to 91.1%) in the ceftaroline group and 88.6% (75.4% to 96.2%) in the comparator. For Staphylococcus aureus the clinical cure rates were slightly higher in the comparator group than in the ceftaroline (Table 14). At the EOT visit, in the MITT population, the clinical cure rate (95% CI) was 87.8% (79.6% to 93.5%) for ceftaroline and 93.3% (81.7% to 98.6%) for comparator. One subject in each group experienced a clinical relapse at LFU after having been designated as cured at TOC. In the mMITT population, 66 (85.7%) subjects in the ceftaroline group and 34 (89.5%) in the comparator had a favourable microbiological response at TOC. Per pathogen microbiological response was similar for the two treatment groups but there were too few bacterial isolates to enable proper comparison (Table 15).

Table 14. Clinical Cure Rates at the Test-of-cure Visit by Baseline Pathogen from the Primary Infection Site or Blood—ME Population

Baseline Pathogen	*Ceftaroline n/N (%)*	*Linezolid plus Aztreonam n/N (%)*
Gram-positive organisms[a]	53/57 (93.0)	31/32 (96.9)
Staphylococcus aureus[b]	51/55 (92.7)	31/32 (96.9)
MRSA	38/40 (95.0)	19/19 (100.0)
MSSA	13/15 (86.7)	12/13 (92.3)
Streptococcus agalactiae	1/2 (50.0)	0
Streptococcus bovis	1/2 (50.0)	0

[34] Sponsor clarification: "These numbers related to those who completed the study drug, not those who completed the study."

Table 15.Favorable Per-pathogen Microbiological Response at the Test-of-cure Visit from the Primary Infection Site or Blood—ME Population

Baseline Pathogen	*Ceftaroline n/N (%)*	*Linezolid plus Aztreonam n/N (%)*
Gram-positive organisms (aerobes)	54/57 (94.7)	31/32 (96.9)
Staphylococcus aureus[a]	52/55 (94.5)	31/32 (96.9)
MRSA	39/40 (97.5)	19/19 (100.0)
MSSA	13/15 (86.7)	12/13 (92.3)
Streptococcus agalactiae	1/2 (50.0)	0
Streptococcus bovis	1/2 (50.0)	0
Monomicrobial gram-positive infections	54/56 (96.4)	31/32 (96.9)
Polymicrobial gram-positive infections	0/1 (0)	0
Gram-negative organisms (aerobes)	3/4 (75.0)	0
Escherichia coli	1/2 (50.0)	0
Proteus mirabilis	2/2 (100.0)	0
Pseudomonas aeruginosa	1/2 (50.0)	0
Monomicrobial gram-negative infections	2/3 (66.7)	0
Polymicrobial gram-negative infections	1/1 (100.0)	0
Mixed gram-positive and gram-negative infections	1/2 (50.0)	1/1 (100.0)

Abbreviations: ME = microbiologically evaluable; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; n = number of subjects within a specific category, favorable response includes eradication and presumed eradication; N = number of subjects with the specified pathogen in the ME Population at baseline.

a Subjects with a baseline pathogen of *Staphylococcus aureus* and no susceptibility testing are included only in the overall *Staphylococcus aureus* line. Subjects with the same pathogen from the primary infection site and blood are counted once for that pathogen at the worst response.

Note: Clinical cure rates are shown only for those pathogens isolated in two or more subjects in either treatment group at baseline.

Note: Subjects with a mixture of both gram-positive and gram-negative pathogens identified at baseline were counted in the "Mixed gram-positive and gram-negative infections" row only, and not in any of the individual gram-positive or gram-negative rows.

6.1.2. Other efficacy studies

There were no additional efficacy studies for the indication of cSSTI.

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

A pooled analysis of efficacy was submitted. Study P903-06 and Study P903-07 were identical in design and conduct. The following results were obtained from a pooled analysis of efficacy for the MITT population:

- Clinical cure at TOC was reported for 595 (85.9%) subjects with ceftaroline and 586 (85.5%) with comparator, Weighted Difference (95% CI) 0.3% (-3.4% to 4.0%).
- Clinical cure at EOT was reported for 626 (90.3%) subjects with ceftaroline and 615 (89.8%) with comparator, Weighted Difference (95% CI) 0.6% (-2.6% to 3.8%).
- Clinical cure at TOC for subjects with MSSA (mMITT population) was reported for 221 (90.2%) subjects with ceftaroline and 233 (90.3%) with comparator, Weighted Difference (95% CI) -0.1% (-5.5% to 5.2%).
- Clinical cure at TOC for subjects with MRSA (mMITT population) was reported for 155 (86.6%) subjects with ceftaroline and 124 (82.1%) with comparator, Weighted Difference (95% CI) 4.4% (-3.4% to 12.6%),

- Clinical cure at TOC for subjects with MRSA (mMITT population) was reported for 429 (87.7%) subjects with ceftaroline and 420 (86.6%) with comparator, Weighted Difference (95% CI) 1.1 (-3.1 to 5.4).
- Four subjects in the ceftaroline group and none in the comparator had a pathogen showing decreased susceptibility through to the TOC visit.
- Clinical cure rate in the CE population for subjects over 65 years of age appeared to be poorer for ceftaroline than comparator but better for subjects of African American ethnicity.

For all four efficacy studies, the following results were obtained from pooled analysis:

- Clinical cure at TOC was reported for 654 (86.1%) subjects with ceftaroline and 612 (85.4%) with comparator, Weighted Difference (95% CI) 0.7% (-2.9% to 4.3%).
- Clinical cure at EOT was reported for 654 (86.1%) subjects with ceftaroline and 612 (85.4%) with comparator, Weighted Difference (95% CI) 0.7% (-2.4% to 3.8%).
- Clinical cure at TOC for subjects with MSSA (mMITT population) was reported for 246 (90.4%) subjects with ceftaroline and 245 (90.1%) with comparator, Weighted Difference (95% CI) 0.4% (-4.8% to 5.5%).
- Clinical cure at TOC for subjects with MRSA (mMITT population) was reported for 159 (85.9%) subjects with ceftaroline and 129 (82.2%) with comparator, Weighted Difference (95% CI) not reported.
- Clinical cure at TOC for subjects with aerobic Gram positive organisms (mMITT population) was reported for 470 (87.7%) subjects with ceftaroline and 440 (86.4%) with comparator, Weighted Difference (95% CI) 1.3 (-2.8 to 5.4).

6.2. Clinical Efficacy in CAP

6.2.1. Pivotal efficacy studies

6.2.1.1. Study P903-08

6.2.1.1.1. Study design, objectives, locations and dates

Study P903-08 was a multicentre, randomised, double blind, comparator controlled (ceftriaxone), parallel group, Phase III, non-inferiority study of ceftaroline in community acquired pneumonia. The study was sponsored by Cerexa Inc and conducted in Asia, Western Europe, Eastern Europe, Latin America, South Africa and the US from January 2008 to December 2008.

6.2.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Subjects were male or female 18 years and older
- Subjects had CABP that met the all following criteria:
  - Radiographically-confirmed pneumonia (new or progressive pulmonary infiltrate(s) on chest radiograph (CXR) or chest computed tomography (CT) scan consistent with bacterial pneumonia)
  - Acute illness (less than or equal to 7 days' duration) with at least three of the following clinical signs or symptoms consistent with a lower respiratory tract infection:
- New or increased cough
- Purulent sputum or change in sputum character

- Auscultatory findings consistent with pneumonia (for example, rales, egophony, findings of consolidation)
- Dyspnoea, tachypnoea, or hypoxaemia (O_2 saturation < 90% on room air or pO_2 <60 mmHg)
- Fever greater than 38ºC oral (>38.5ºC rectally or tympanically) or hypothermia (<35ºC)
- White blood cell (WBC) count greater than 10,000 cells/mm^3 or less than 4,500 cells/mm^3
- Greater than 15% immature neutrophils (bands) irrespective of WBC count
  - PORT score greater than 70 and less than or equal to 130 (that is, PORT Risk Class III or IV)
- The subject required initial hospitalization, or treatment in an emergency room or urgent care setting, by the standard of care
- The subject had an infection that required initial treatment with IV antimicrobials
- Female subjects of child-bearing potential and those who were less than 2 years postmenopausal, using highly effective methods of birth control while participating in the study

The exclusion criteria included:

- A PORT score ≤70 (PORT Risk Class I or II), PORT score >130 (PORT Risk Class V), or required admission to an intensive care unit
- CABP suitable for outpatient therapy with an oral antimicrobial agent
- Confirmed or suspected respiratory tract infections attributable to sources other than community-acquired bacterial pathogens (eg, ventilator-associated pneumonia, hospital-acquired pneumonia, visible/gross aspiration pneumonia, suspected viral, fungal, or mycobacterial infection of the lung)
- Non-infectious causes of pulmonary infiltrates
- Pleural empyema (not including non-purulent para-pneumonic effusions)
- Microbiologically documented infection with a pathogen known to be resistant to ceftriaxone, or epidemiological or clinical context suggesting high likelihood of a ceftriaxone-resistant “typical” bacterial pathogen
- Infection with an atypical organism (M. pneumoniae, C. pneumoniae, Legionella spp.)
- Previous treatment with an antimicrobial for treatment of CABP within 96 hrs
- Failure of ceftriaxone (or other third-generation cephalosporin) as therapy for this episode of CABP
- History of any hypersensitivity or allergic reaction to any β-lactam antimicrobial
- History of any hypersensitivity or allergic reaction to clarithromycin or any macrolide/ketolide
- Inability to take oral clarithromycin
- Requirement for concomitant therapy with any drug known to exhibit a contraindicated drug-drug interaction with clarithromycin; or labelled contraindication to use of clarithromycin
- Past or current history of epilepsy or seizure disorder
- Requirement for concomitant antimicrobial or systemic antifungal therapy for any reason

- Neoplastic lung disease, cystic fibrosis, progressively fatal disease, chronic neurological disorder preventing clearance of pulmonary secretions, or life expectancy of less than or equal to 3 months
- Probenecid administration within 3 days before initiation of study drug therapy or requirement for concomitant therapy with probenecid
- Infections or conditions requiring concomitant systemic corticosteroids
- Severely impaired renal function (CrCl ≤ 30 mL/min) estimated by the Cockroft-Gault formula
- Evidence of significant hepatic, hematological, or immunologic disease
- Evidence of immediately life-threatening disease
- Residence in a nursing home or assisted living facility that provided 24-hr medical supervision
- Women who were pregnant or nursing

6.2.1.1.3. Study treatments

The study treatments were:

1. Ceftaroline fosamil 600 mg (two doses of 300 mg given consecutively, each IV over 30 minutes in order to maintain blinding, q12h (reduced to two doses of 200 mg q12h if CrCl >30 mL/min and ≤50 mL/min)
2. Ceftriaxone 1 g IV over 30 minutes q24h, with saline placebo over 30 min to maintain blinding

Two doses of oral clarithromycin, 500 mg q12h, were administered in both treatment groups as adjunctive treatment. The treatment duration was for 5 to 7 days.

6.2.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the per-subject clinical cure rate at TOC in the CE and MITTE Populations. The secondary efficacy outcome measures were:

- Clinical response at EOT in the MITTE and CE populations
- Microbiological success rate at TOC in the mMITT, mMITTE and ME populations
- Overall success rate at TOC in the MITTE and CE populations
- Clinical and microbiological response by pathogen at TOC in the mMITTE and ME populations
- Clinical relapse at LFU
- Microbiological reinfection/ recurrence at LFU

The safety outcome measures were AEs, laboratory tests, vital signs and ECGs. The schedule of study visits was summarised in the study report. TOC was 8 to 15 days after last dose of study drug. LFU was 21 to 35 days after last dose of study drug.

The clinical outcome categories were:

- Clinical Cure: Total resolution of all signs and symptoms of pneumonia (that is, CABP), or improvement to such an extent that further antimicrobial therapy was not necessary
- Clinical Failure: Any of the following:
  - Persistence, incomplete clinical resolution, or worsening in signs and symptoms of CABP that required alternative antimicrobial therapy

  - Treatment-limiting AE leading to discontinuation of study drug therapy, when subject required alternative antimicrobial therapy to treat the pneumonia
  - Death wherein pneumonia (that is, CABP) was considered causative
- Indeterminate: Study data were not available for evaluation of efficacy, for any reason including treatment change before completing at least 48 hr of study drug therapy; death wherein pneumonia was clearly non-contributory, loss to follow-up, or extenuating circumstances that precluded classification as a cure or failure.

The radiological outcome categories were:

- Radiographic Success: CXR or chest CT scan was resolved, improved, or stable compared to the baseline CXR or CT scan
- Radiographic Failure: CXR or chest CT scan had unequivocally worsened compared to the baseline CXR or CT scan
- Indeterminate: CXR or CT scan not performed, missing, or could not be adequately interpreted to determine an outcome

The microbiological outcome categories were:

- Eradication: An appropriate source specimen demonstrated absence of the original baseline pathogen
- Presumed eradication: An appropriate source specimen was not available to culture and the subject was assessed as a clinical cure
- Persistence: An appropriate source specimen demonstrated continued presence of the original baseline pathogen
- Presumed persistence: An appropriate source specimen was not available to culture and the subject was assessed as a clinical failure
- Indeterminate: An appropriate source specimen was not available to culture and the subject's clinical response was assessed as indeterminate

6.2.1.1.5. Randomisation and blinding methods

Subjects were block randomised to treatment group using IVRS, stratified by country and severity of disease, in the ratio of 1:1 to ceftaroline or ceftriaxone.

6.2.1.1.6. Analysis populations

- The ITT population consisted of all randomised subjects.
- The MITT population consisted of all randomised subjects who received any amount of study drug. The MITT population was used for safety analyses.
- The MITTE population consisted of all subjects in PORT Risk Class III or IV in the MITT population.
- The mMITT population consisted of all subjects in the MITT population who met the minimal disease criteria for CABP, whose PORT Risk Class was II, III, or IV and who had at least one typical bacterial organism consistent with a CABP pathogen identified from an appropriate microbiological specimen (for example, blood, sputum or pleural fluid).
- The mMITTE population consisted of all subjects with a PORT Risk Class of III or IV in the mMITT population.
- The CE population consisted of all subjects in the MITTE population who also met the minimal disease criteria for CABP and for whom sufficient information regarding the CABP was available to determine the subject's outcome.

6.2.1.1.7. Sample size

The sample size was based on a point estimate of the overall (combined clinical and radiographic) success rate of 90% in the CE Population in both the ceftaroline and ceftriaxone groups. The non-inferiority margin was 10% which ensured that ceftaroline maintained a significant fraction of the treatment effect of antibiotics for CABP over a putative placebo. Using a non-inferiority margin of 10%, 90% power and a two-sided alpha of 0.05, based on the sample size determination method of Farrington and Manning (1990), a total of 205 evaluable subjects in each treatment group was required. Assuming that approximately 60 subjects in PORT Risk Class II were enrolled and that 75% of the randomised population was evaluable for the CE Population, a total sample size of 610 subjects was required: 305 subjects in each treatment group.

6.2.1.1.8. Statistical methods

Hypothesis tests were performed using differences in rates and 95% CI.

6.2.1.1.9. Participant flow

There were 305 subjects randomised to ceftaroline and 309 to ceftriaxone. In the MITT group there were 299 subjects in the ceftaroline group and 307 in the ceftriaxone. In the MITTE group there were 291 subjects in the ceftaroline group and 300 in the ceftriaxone. In the CE group there were 224 subjects in the ceftaroline group and 234 in the ceftriaxone. In the mMITT group there were 75 subjects in the ceftaroline group and 82 in the ceftriaxone. In the mMITTE group there were 75 subjects in the ceftaroline group and 80 in the ceftriaxone. In the ME group; there were 69 subjects in the ceftaroline group and 71 in the ceftriaxone. The patterns of exclusion were similar for the two treatment groups. A total of 277 (95.2%) subjects in the ceftaroline group and 283 (94.3%) in the ceftriaxone completed the study.

6.2.1.1.10. Baseline data

There were 378 (64.0%) males, 213 (36.0%) females and the age range was 18 to 94 years. The treatment groups were similar in demographic and baseline characteristics. Structural lung disease, prior pneumonia and alcohol abuse were more common in the ceftaroline group. Prior respiratory signs and symptoms were also slightly more common in the ceftaroline group. The signs and symptoms of CABP were similar for the two treatment groups at baseline. Baseline severity was similar for the two treatment groups. Staphylococcus aureus isolates were less common in the ceftaroline group, 10 (13.3%) subjects with isolates compared with 14 (17.5%) in the ceftriaxone. Aerobic Gram negative isolates were more common in the ceftaroline group, 44 (58.7%) subjects with isolates compared with 44 (55.0%) in the ceftriaxone. The Staphylococcal isolates appear to have been sensitive to ceftaroline but relatively resistant to ceftriaxone. The MICs for ceftriaxone of the Staphylococcal isolates were in the range 2 to 4 µg/mL and the MIC90 was 4 µg/mL. Systemic antibiotics were received in the 96 hr prior to randomisation by 143 (47.8%) subjects in the ceftaroline group and 146 (47.6%) in the ceftriaxone. Additional systemic antibiotics were received from randomisation to TOC by 43 (14.8%) subjects in the ceftaroline group and 57 (19.0%) in the ceftriaxone.

6.2.1.1.11. Results for the primary efficacy outcome

Non-inferiority was demonstrated for ceftaroline in comparison with ceftriaxone. In the CE population, clinical cure was recorded for 194 (86.6%) subjects in the ceftaroline group and 183 (78.2%) in the ceftriaxone, difference in rates (95% CI) 8.4% (1.4% to 15.4%). In the MITTE population, clinical cure was recorded for 244 (83.8%) subjects in the ceftaroline group and 233 (77.7%) in the ceftriaxone, difference in rates (95% CI) 6.2% (–0.2% to 12.6%). Clinical cure rates were lower for ceftaroline in Brazil, Germany and Switzerland. The cure rate for ceftaroline was not adversely affected by demographic or baseline characteristics.

6.2.1.1.12. Results for other efficacy outcomes

Clinical response at EOT was greater in the ceftaroline group in the MITTE and CE populations. In the MITTE population, clinical cure at EOT was recorded for 253 (86.9%) subjects in the ceftaroline group and 242 (80.7%) in the ceftriaxone, difference in rates (95% CI) 6.3% (0.3% to 12.3%). There was no significant difference in microbiological success rate at TOC in the mMITT, mMITTE and ME populations. In the mMITT population, clinical cure at TOC was recorded for 66 (88.0%) subjects in the ceftaroline group and 65 (79.3%) in the ceftriaxone, difference in rates (95% CI) 8.7% (-3.1% to 20.5%). There was no significant difference in overall success rate at TOC in the MITTE population but ceftaroline had a higher success rate in the CE population (Table 7.2.1.1.17). In the CE population, for overall success, cure at TOC was recorded for 194 (86.6%) subjects in the ceftaroline group and 183 (78.2%) in the ceftriaxone, difference in rates (95% CI) 8.4% (1.4% to 15.4%). Clinical and microbiological response by pathogen at TOC in the ME population was better in the ceftaroline population for Staphylococcus aureus and Streptococcus pneumoniae. Clinical relapse at LFU occurred in three (1.2%) subjects in the ceftaroline group and three (1.3%) in the ceftriaxone. Median (95% CI) time to defervescence of fever, for the MITTE population was 2.0 (2.0 to 3.0) days for both treatment groups. Median (95% CI) time to resolution of hypoxia was 2.0 (2.0 to 3.0) days in the ceftaroline group and 3.0 (2.0 to 3.0) days in the ceftriaxone. In the MITTE population, the 30-day mortality rate was 1.4% (four subjects) in the ceftaroline group and 1.7% (five subjects) in the ceftriaxone group. The total mortality rate was 1.7% (five subjects) in the ceftaroline group and 1.7% (five subjects) in the ceftriaxone group. There were no subjects in the MITTE population with microbiological reinfection/ recurrence at LFU.

6.2.1.2. Study P903-09

6.2.1.2.1. Study design, objectives, locations and dates

Study P903-09 was a multicentre, randomised, double blind, comparator controlled (ceftriaxone), parallel group, Phase III, non-inferiority study of ceftaroline in community acquired pneumonia. The study was similar in design to Study P903-08, the main difference being the use of clarithromycin as adjuvant treatment in Study P903-08. The study was sponsored by Cerexa Inc and conducted in Asia, Western Europe, Eastern Europe and Latin America from July 2007 to August 2008.

6.2.1.2.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria were the same as for Study P903-08, except that the following were not listed as exclusion criteria:

- History of any hypersensitivity or allergic reaction to clarithromycin or any macrolide/ketolide
- Inability to take oral clarithromycin
- Requirement for concomitant therapy with any drug known to exhibit a contraindicated drug-drug interaction with clarithromycin; or labelled contraindication to use of clarithromycin

6.2.1.2.3. Study treatments

The study treatments were:

1. Ceftaroline fosamil 600 mg (two consecutive doses of 300 mg, IV over 30 minutes, q12h (reduced to 400 mg (two consecutive doses of 200 mg) q12h if CrCl >30 mL/min and ≤50 mL/min)
2. Ceftriaxone 1 g IV over 30 minutes q24h, with saline placebo to maintain blinding

Two doses of oral clarithromycin, 500 mg q12h, were administered in both treatment groups as adjunctive treatment. The treatment duration was for 5 to 7 days.

6.2.1.2.4. Efficacy variables and outcomes

The efficacy variables, outcomes, analysis populations and statistical methods were the same as for Study P903-08.

6.2.1.2.5. Sample size

The sample size was based on a point estimate of the overall (combined clinical and radiographic) success rate of 90% in the CE population in both the ceftaroline and ceftriaxone groups. The non-inferiority margin was 10% which ensured that ceftaroline maintained a significant fraction of the treatment effect of antibiotics for CABP over a putative placebo. Using a non-inferiority margin of 10%, 90% power and a two-sided alpha of 0.05, based on the sample size determination method of Farrington and Manning (1990), a total of 205 evaluable subjects in each treatment group was required. Assuming that approximately 76 subjects in PORT Risk Class II were enrolled and that 75% of the randomised population was evaluable for the CE Population, a total sample size of 626 subjects was required: 313 subjects in each treatment group.

6.2.1.2.6. Participant flow

There were 317 subjects randomised to ceftaroline and 310 to ceftriaxone. In the MITT population there were 315 subjects in the ceftaroline group and 307 in the ceftriaxone. In the MITTE population there were 289 subjects in the ceftaroline group and 273 in the ceftriaxone. In the CE population there were 235 subjects in the ceftaroline group and 215 in the ceftriaxone. In the mMITT population there were 90 subjects in the ceftaroline group and 88 in the ceftriaxone. In the mMITTE population there were 90 subjects in the ceftaroline group and 88 in the ceftriaxone. In the ME population there were 85 subjects in the ceftaroline group and 76 in the ceftriaxone. The reasons for exclusion from the analysis populations was summarised in the study report. A total of 271 (93.8%) subjects in the ceftaroline group and 246 (90.1%) in the ceftriaxone completed the study and the reasons for discontinuation are summarised in Table 16.

Table 16. Premature Discontinuations from Study Drug Therapy and Withdrawals From the Study—MITTE Population

	Ceftaroline (N = 289) n (%)	*Ceftriaxone (N = 273) n (%)*	*Total (N = 562) n (%)*
Completed Study Drug	271 (93.8)	246 (90.1)	517 (92.0)
Prematurely Discontinued from Study Drug	18 (6.2)	27 (9.9)	45 (8.0)
Reasons for Premature Discontinuation			
Adverse event	7 (2.4)	8 (2.9)	15 (2.7)
At request of sponsor/investigator	0	1 (0.4)	1 (0.2)
Insufficient therapeutic effect	8 (2.8)	12 (4.4)	20 (3.6)
Clinical worsening	4 (1.4)	5 (1.8)	9 (1.6)
Lack of clinical progress	3 (1.0)	5 (1.8)	8 (1.4)
Due to resistant pathogen	1 (0.3)	2 (0.7)	3 (0.5)
Withdrew consent	2 (0.7)	4 (1.5)	6 (1.1)
Other	1 (0.3)	2 (0.7)	3 (0.5)
Completed Study	259 (89.6)	248 (90.8)	507 (90.2)
Withdrew from Study	30 (10.4)	25 (9.2)	55 (9.8)
Reason for Withdrawal from Study			
Adverse event	2 (0.7)	2 (0.7)	4 (0.7)
Noncompliance with study treatment regimen	0	1 (0.4)	1 (0.2)
At request of sponsor/investigator	1 (0.3)	1 (0.4)	2 (0.4)
Withdrew consent	4 (1.4)	8 (2.9)	12 (2.1)
Lost to follow-up	16 (5.5)	8 (2.9)	24 (4.3)
Other	1 (0.3)	0	1 (0.2)
Death	6 (2.1)	5 (1.8)	11 (2.0)

Abbreviations: MITTE = Modified Intent-to-Treat Efficacy.

6.2.1.2.7. Baseline data

There were 350 (62.3%) males, 212 (37.7%) females and the age range was 18 to 99 years. The treatment groups were similar in demographic and baseline characteristics. A higher proportion of subjects in the ceftaroline group had a relevant prior medical history: 147 (50.9%) subjects compared with 120 (44.0%). Prior respiratory signs and symptoms were similar for the two treatment groups. Respiratory signs and symptoms at baseline were similar for the two groups. Disease severity was similar at baseline. Of the bacterial isolates, the most commonly isolates were: Streptococcus pneumoniae 46.1%, Staphylococcus aureus 17.4% and Haemophilus influenzae 16.3%. Fifteen subjects in the ceftaroline group and eleven in the ceftriaxone had positive blood cultures. Systemic antibacterial treatment prior to randomisation was received by 113 (35.9%) subjects in the ceftaroline group and 130 (42.3%) in the ceftriaxone. Additional systemic antibiotics from randomisation to TOC were received by 47 (16.3%) subjects in the ceftaroline group and 60 (22.0%) in the ceftriaxone. The Staphylococcus aureus isolates had greater susceptibility to ceftaroline than ceftriaxone.

6.2.1.2.8. Results for the primary efficacy outcome

Non-inferiority was demonstrated for ceftaroline in comparison with ceftriaxone. In the CE population, clinical cure was recorded for 193 (82.1%) subjects in the ceftaroline group and 166 (77.2%) in the ceftriaxone, difference in rates (95% CI) 4.9% (-2.5% to 12.5%). In the MITTE population, clinical cure was recorded for 235 (81.3%) subjects in the ceftaroline group and 206 (75.5%) in the ceftriaxone, difference in rates (95% CI) 5.9% (-1.0% to 12.7%). Clinical cure rates were lower for ceftaroline in Hungary and India but there were few subjects included from

those countries. The cure rate for ceftaroline was not adversely affected by demographic or baseline characteristics (Table 17).

Table 17. Clinical Cure Rate at Test-of-Cure by Subgroups—CE Population

Baseline Characteristic	*Ceftaroline n/N1 (%)*	*Ceftriaxone n/N1 (%)*
Age (years) Group		
< 65	103/122 (84.4)	86/112 (76.8)
≥ 65	90/113 (79.6)	80/103 (77.7)
< 75	149/178 (83.7)	136/171 (79.5)
≥ 75	44/57 (77.2)	30/44 (68.2)
Sex, n (%)		
Male	113/142 (79.6)	105/140 (75.0)
Female	80/93 (86.0)	61/75 (81.3)
Ethnicity, n (%)		
Hispanic	33/37 (89.2)	29/36 (80.6)
Non-Hispanic	160/198 (80.8)	137/179 (76.5)
Race, n (%)		
White	186/227 (81.9)	162/210 (77.1)
American Indian or Alaska Native	4/4 (100%)	3/4 (75%)
Asian	2/3 (66.7)	1/1 (100.0)
Black or African-American	0/0	0/0
Native Hawaiian or other Pacific Islander	0/0	0/0
Other	1/1 (100.0)	0/0
CURB-65[a]		
0	21/26 (80.8)	19/27 (70.4)
1	67/84 (79.8)	72/89 (80.9)
2	84/102 (82.4)	56/72 (77.8)
3	19/21 (90.5)	15/22 (68.2)
4	2/2 (100.0)	4/5 (80.0)
5	0/0	0/0
PORT Risk Class		
III	113/137 (82.5)	104/132 (78.8)
IV	80/98 (81.6)	62/83 (74.7)
Renal Status [based on CrCl (mL/min)]		
Normal (> 80)	83/96 (86.5)	82/104 (78.8)
Mild (50 < CrCl ≤ 80)	72/92 (78.3)	57/75 (76.0)
Moderate (30 < CrCl ≤ 50)	26/33 (78.8)	21/26 (80.8)
Severe (≤ 30)	8/9 (88.9)	3/5 (60.0)
Presence of Bacteremia		
YES	9/13 (69.2)	6/10 (60.0)
NO	184/222 (82.9)	160/205 (78.0)

Abbreviations: CE = clinically evaluable; CrCl = creatinine clearance; PORT = Pneumonia Outcomes Research Team.

a CURB - 65 ranges from 0 – 5 where 1 point is given for each of the following at baseline: confusion, respiratory rate ≥ 30bpm, urea > 7 mmol/L, and SBP < 90 mm Hg or DBP ≤ 60 mm Hg.

6.2.1.2.9. Results for other efficacy outcomes

Clinical response at EOT was greater in the ceftaroline group in the MITTE and CE populations. In the MITTE population, clinical cure at EOT was recorded for 249 (86.2%) subjects in the ceftaroline group and 215 (88.8%) in the ceftriaxone, difference in rates (95% CI) 7.4% (1.1% to 13.8%). There was no significant difference in microbiological success rate at TOC in the mMITT, mMITTE and ME populations. In the mMITT population, favourable response at TOC was recorded for 81 (81.8%) subjects in the ceftaroline group and 83 (81.4%) in the ceftriaxone, difference in rates (95% CI) 0.4% (-10.5% to 11.3%). There was no significant difference in overall success rate at TOC in the MITTE or CE populations. In the MITTE population, for overall success, cure at TOC was recorded for 234 (81.0%) subjects in the

ceftaroline group and 206 (75.5%) in the ceftriaxone, difference in rates (95% CI) 5.5% (-1.3% to 12.4%). Clinical response by pathogen at TOC in the ME population was better in the ceftaroline population for Staphylococcus aureus and Streptococcus pneumoniae and microbiological response was better for Streptococcus pneumoniae. Clinical relapse at LFU occurred in five (2.1%) subjects in the ceftaroline group and two (1.0%) in the ceftriaxone. Median (95% CI) time to defervescence of fever, for the MITTE population was 2.0 (2.0 to 2.0) for the ceftaroline group and 2.0 (2.0 to 3.0) days for the ceftriaxone. Median (95% CI) time to resolution of hypoxia was 2.0 (2.0 to 3.0) days for both treatment groups. In the MITTE population, the 30-day mortality rate was 2.8% (eight subjects) in the ceftaroline group and 1.6% (five subjects) in the ceftriaxone group. The total mortality rate was 3.1% (nine subjects) in the ceftaroline group and 1.7% (five subjects) in the ceftriaxone group. There were no subjects in the MITTE population with microbiological reinfection/ recurrence at LFU. No subject in the ceftaroline group had a pathogen with decreasing ceftaroline susceptibility.

6.2.2. Analyses performed across trials (pooled analyses and meta-analyses)

A pooled analysis of the efficacy data from Study P903-08 and Study P903-09 was provided in tabular form. With regard to the efficacy outcome measures:

- In the MITTE population ceftaroline was superior to ceftriaxone for clinical response at TOC: 479 (82.6%) subjects in the ceftaroline group compared with 439 (76.6%) in the ceftriaxone, weighted difference (95% CI) 6.0% (1.4% to 10.7%).
- In the mMITTE population ceftaroline for Gram positive organisms was superior to ceftriaxone for clinical response at TOC: 77 (83.7%) subjects in the ceftaroline group compared with 64 (66.0%) in the ceftriaxone, weighted difference (95% CI) 17.9% (5.5% to 29.8%). However, for Gram negative organisms there was no difference between treatments: 75 (83.3%) subjects in the ceftaroline group compared with 76 (83.5%) in the ceftriaxone, weighted difference (95% CI) -0.2% (-11.4% to 10.8%).
- Response rates were not influenced by demographic factors, in confirmation of the individual study results.

There were insufficient subjects with MRSA to perform a comparison.

6.3. Australian surveillance data

The surveillance of Australian isolates indicated excellent activity for ceftaroline against Staphylococcus aureus, including MRSA and Streptococcus pneumoniae, including penicillin resistant strains. There was also excellent activity against Haemophilus influenzae. However, ceftaroline had limited activity against Gram negative organisms and ESBL producing strains were resistant. The isolates were obtained from major hospitals widely distributed in Australia.

A surveillance report of isolates from the Asia Pacific region, including Australia and New Zealand, was provided as Ceftaroline-M1-002-09-AZ-03. This report indicated sensitivity of Staphylococcus aureus and Streptococcus pneumonia isolates from the region and also Australia. Coagulase negative Staphylococcus (CoNS) isolates also showed good sensitivity to ceftaroline but Enterococcus isolates were all resistant. [information redacted]

6.4. Evaluators conclusions on efficacy

6.4.1. Evaluator's conclusions on clinical efficacy for cSSTI

In Study P903-06 non-inferiority was demonstrated in comparison with vancomycin:

- Clinical cure rates appeared to be worse for ceftaroline in comparison with vancomycin in subjects >75 years age. There also appeared to be a poorer response for Gram negative organisms.[35]

In Study P903-07 non-inferiority was also demonstrated for ceftaroline in comparison with vancomycin. However, in this study clinical cure rates appeared to be better for ceftaroline in comparison with vancomycin in subjects >75 years age. There also appeared to be a poorer response for Gram negative organisms.[36]

Although Study P903-03 had insufficient sample size for hypothesis testing, the results supported the efficacy of ceftaroline in comparison with vancomycin in subjects with cSSTI.

Study P903-19 investigated a different route of administration (intramuscular) and used linezolid as a comparator. Response rates appeared to be poorer for intramuscular ceftaroline than linezolid or intravenous ceftaroline, when compared with the results from the other efficacy studies. However, the Sponsor has not requested approval of the intramuscular administration route in the present application.

The pooled analysis of the efficacy studies supported the efficacy of ceftaroline for the treatment of cSSTI due to MRSA. However, four subjects in the ceftaroline group and none in the comparator had a pathogen showing decreased susceptibility through to the TOC visit.[37]

In the pivotal efficacy studies, the non-inferiority criteria were sufficiently robust and adequately justified. [information redacted] The outcome measures were well designed. The sampling frame for subject selection was appropriate and resulted in a treatment population sufficiently representative of the treatment population in Australia.

The comparators used in the efficacy studies would not normally be first line treatment for cSSTI in Australia. Such infections would normally be treated with flucloxacillin as a first line agent. Vancomycin would be used as a second line agent and for patients with penicillin allergy. Linezolid would normally be reserved as a third line agent. Aztreonam would not normally be used to treat cSSTI in Australia. {information redacted]

6.4.2. Evaluator's conclusions on clinical efficacy for CAP

In Study P903-08, non-inferiority was demonstrated for ceftaroline in comparison with ceftriaxone, when clarithromycin was also used as adjunctive treatment. Response was not influenced by baseline demographic characteristics. Clinical response was better in the ceftaroline population for Staphylococcus aureus and Streptococcus pneumoniae.

In Study P903-09, non-inferiority was demonstrated for ceftaroline in comparison with ceftriaxone, when clarithromycin was not used as adjunctive treatment. Response was not influenced by baseline demographic characteristics. Clinical response was better in the ceftaroline population for Staphylococcus aureus and Streptococcus pneumoniae.

Although superiority testing was not intended in the study protocols, the pooled analysis indicated superiority for ceftaroline in comparison with ceftriaxone. In the MITTE population ceftaroline was superior to ceftriaxone for clinical response at TOC: 479 (82.6%) subjects in the

[35] Sponsor clarification: "Ceftaroline showed a lower clinical cure rate than the comparator for overall Gram-negative organisms in the pooled cSSTI studies (refer Table 3 of the PI), which included patients infected with *P. aeroginosa* and *Proteus* spp. Clinical cure rates for ceftaroline were numerically higher than the comparator for some Gram-negative organisms (Table 3 of the PI)."

[36] Sponsor clarification: "Ceftaroline showed a lower clinical cure rate than the comparator for overall Gram-negative organisms in the pooled cSSTI studies (refer Table 3 of the PI), which included patients infected with *P. aeroginosa* and *Proteus* spp. Clinical cure rates for ceftaroline were numerically higher than the comparator for some Gram-negative organisms (Table 3 of the PI)"

[37] Sponsor clarification: "The pathogens in these 4 cases were *S. agalactiae, P. aeruginosa, E. cloacae* and *P. mirabilis.* Only 1 pathogen (*E. cloacae*) showed decreased susceptibility on repeated testing."

ceftaroline group compared with 439 (76.6%) in the ceftriaxone, weighted difference (95% CI) 6.0% (1.4% to 10.7%).

In the pivotal efficacy studies, the non-inferiority criteria were sufficiently robust and adequately justified. [information redacted] The outcome measures were well designed. The sampling frame for subject selection was appropriate and resulted in a treatment population sufficiently representative of the treatment population in Australia.

The comparator used in the efficacy studies (ceftriaxone) would not normally be first line treatment for CAP in Australia. Such infections would normally be treated with penicillin as a first line agent, unless the patient's condition was severe. Ceftriaxone would usually be used for hospital acquired pneumonia rather than CAP in the Australian setting.

7. Clinical safety

7.1. Studies providing evaluable safety data

Safety data were provided from all of the clinical studies evaluated above and which were conducted by the sponsor in support of pharmacokinetics, pharmacodynamics and efficacy.

7.2. Pivotal studies that assessed safety as a primary outcome

There were no additional studies assessing safety as the primary outcome.

7.3. Patient exposure

There were a total of 1470 subjects exposed to ceftaroline fosamil in Phase II and Phase III trials during the development program. This included 613 with CAP and 857 with cSSTI. There were no subjects aged less than 18 years included in the Phase II and Phase III trials. There were 402 subjects age 65 years or more, including 188 subjects aged 75 years or more. There were 117 subjects with creatinine clearance >30 and ≤50 mL/min and 15 subjects with creatinine clearance ≤30 mL/min. There were 169 subjects with hepatic impairment and 287 with cardiac impairment.

7.3.1. Patient exposure in cSSTI

In Study P903-03, there were 67 subjects treated with ceftaroline fosamil. The duration of treatment was, median (range), 6.7 (0.4 to 19.5) days in the ceftaroline group and 7.4 (2.0 to 20.5) in the comparator.

In Study P903-06, 351 subjects with cSSTI were exposed to ceftaroline with a median (range) duration of exposure of 7.0 (0.5 to 18.0) days. One subject was exposed for 15 days or more.

In Study P903-07, a total of 341 subjects received ceftaroline for the indication of cSSTI. The median (range) duration of exposure was 6.5 (0.5 to 21.0) days.

In Study P903-19, a total of 98 subjects with cSSTI were exposed to ceftaroline 600 mg q12h for a median (range) of 6.50 (0.5 to 13.0) days.

7.3.2. Patient exposure in CAP

In Study P903-08, a total of 298 subjects with CABP were exposed to ceftaroline for a median (range) of 6.5 (0.5 to 7.5) days. No subjects were exposed to ceftaroline for more than 8 days.

In Study P903-09, a total of 315 subjects with CABP were exposed to ceftaroline for a median (range) of 6.0 (1.0 to 7.0) days. No subjects were exposed to ceftaroline for more than 8 days.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Pivotal studies for cSSTI

In Study P903-03, there were 157 TEAEs reported in 41 (61.2%) subjects in the ceftaroline group and 89 in 18 (56.3%) in the comparator. The commonest TEAE in the ceftaroline group was headache, occurring in eleven (16.4%) subjects. Rash was reported in seven (10.4%) subjects.

In Study P903-06, TEAEs were reported in 165 (47.0%) subjects in the ceftaroline group and 167 (48.1%) in the comparator. Nausea, headache and rash were slightly more common in the ceftaroline group but pruritus was more common in the comparator. No seizures were reported during the study. In Study P903-06, two subjects in the ceftaroline group had an increase in QTc >60 ms at EOT. Clostridium difficile infection/colitis was reported for two subjects in the ceftaroline group and one in the comparator.

In Study P903-07, TEAEs were reported in 144 (42.2%) subjects in the ceftaroline group and 159 (46.9%) in the comparator. Pruritus was more common with comparator, 28 (8.3%) subjects compared with 13 (3.8%) in the ceftaroline group. Otherwise the pattern of TEAEs was similar for the two treatment groups. There were no TEAEs related to Clostridium difficile. One subject in the ceftaroline group was reported as having seizures following coronary bypass surgery. There were no potentially clinically significant prolongations of QTcB recorded for the ceftaroline group.

In Study P903-19, TEAEs were reported in 59 (60.2%) subjects in the ceftaroline group and 23 (51.2%) in the comparator. The commonest TEAEs were nausea, occurring in 12 (12.2%) subjects in the ceftaroline group and seven (15.6%) in the comparator; and headache, occurring in ten (10.2%) subjects in the ceftaroline group and eight (17.8%) in the comparator. There were no clinically significant ECG abnormalities.

7.4.1.2. Pivotal studies for CAP

In Study P903-08, TEAEs were reported in 119 (39.9%) subjects in the ceftaroline group and 136 (44.2%) in the ceftriaxone. Diarrhoea was more common in the ceftaroline group, 14 (4.7%) subjects, compared with seven (2.3%) in the ceftriaxone. After diarrhoea, the commonest TEAE in the ceftaroline group was headache, ten (3.4%) subjects. Potentially allergic TEAEs occurred in three (1.0%) subjects in the ceftaroline group and four (1.3%) in the ceftriaxone. Clostridium difficile colitis was not reported for any subject. No seizures were reported. Increase in QTcF ≥60 ms at EOT occurred in eight (1.8%) subjects in the ceftaroline group and six (2.1%) in the ceftriaxone but none of the events in the ceftaroline group was considered to be clinically significant by the Investigators.

In Study P903-09, TEAEs were reported in 169 (53.7%) subjects in the ceftaroline group and 145 (47.2%) in the ceftriaxone. Hypokalaemia and headache occurred to a greater extent in the ceftaroline group, 10 (3.2%) subjects and 11 (3.5%) respectively, compared with the ceftriaxone group, 5 (1.6%) and 5 (1.6%) respectively. Diarrhoea was the most frequently reported TEAE in the ceftaroline group, occurring in twelve (3.8%) subjects. Potentially allergic TEAEs occurred in six (1.9%) subjects in the ceftaroline group and six (2.0%) in the ceftriaxone. No subject with Clostridium difficile associated diarrhoea or colitis was reported. One subject in each treatment group was reported with seizures. A post-baseline increase in QTcF >60 msec was reported in one (0.3%) subject in the ceftaroline group and two (0.7%) in the ceftriaxone.

7.4.1.3. Other studies

In Study CXL-PK-01 in Part A, twelve TEAEs were reported in seven (58.3%) subjects. The most common TEAE was headache in four subjects. In Part B there were 252 TEAEs in 34 (94.4%) subjects that received active treatment and 57 in seven (77.8%) subjects that received placebo.

The commonest TEAEs in Part B were: infusion site pain, 33 (68.8%) subjects; infusion site erythema, 30 (62.5%), infusion site oedema, 19 (39.6%), infusion site induration, 17 (35.4%), headache, eleven (22.9%), infusion site extravasation, ten (20.8%), rash generalised, ten (20.8%) and pruritus generalised, eight (16.7%). There were no clinically significant laboratory test abnormalities and no subject developed antibodies to ceftaroline.

In Study P903-13 there was one TEAE: mild loss of appetite.

Study P903-01 Part 1: ten (28%) of subjects that received ceftaroline fosamil reported TEAEs compared with twelve (25%) in the placebo group. The most common TEAE was headache: four (11%) subjects in the ceftaroline fosamil group and one (8%) in the placebo. In Part 2, twelve (67%) subjects treated with ceftaroline fosamil reported TEAEs compared with six (100%) in the placebo group. The most common TEAE was bruising of the arm: five (28%) subjects in the ceftaroline fosamil group and three in the placebo. Discolouration of urine and odour were reported with the 600 mg q12h dose. All six subjects receiving 600 mg ceftaroline fosamil q12h (1200 mg daily) for 14 days noted their urine had become a deeper yellow within 36 hr of receiving the first dose of ceftaroline fosamil. Change in urine colour was not noted at any other dose level/regimen. In addition four (67%) of the subjects receiving 600 mg ceftaroline fosamil q12h experienced a change in urine odour and three (50%) experienced a change in body odour. These changes were initially noted within the first 2 days of ceftaroline fosamil administration and generally continued until 1 to 2 days after treatment was ceased. Self-limiting rash was reported in one subject receiving 300 mg ceftaroline fosamil q12h for 14 days, in three subjects receiving 600 mg ceftaroline fosamil q12h for 14 days and no subject receiving 800 mg ceftaroline fosamil for 7 days. The distribution and character of each subject's rash were different and plausible non-study drug related etiologies (contact reaction for 2 subjects, viral infection for one subject and poor personal hygiene for one subject) exist for all reported rashes, making a common etiology unlikely. In addition, all rashes resolved while subjects continued receiving ceftaroline fosamil. Injection site pain/discomfort/thrombophlebitis was reported in eight of 18 (44%) subjects in the ceftaroline fosamil groups and one (17%) subjects in the placebo in Part 2 of the study. There were no abnormalities in ECG monitoring or in clinical laboratory parameters.

Study P903-17 in Part A there were twelve TEAEs in nine subjects. The most common TEAEs (each reported in two subjects) were: headache, injection site pain, syncope and urine odour. In Part B there were ten TEAEs in the twelve subjects in the ceftaroline group and four in six in the cefepime. In the ceftaroline group three subjects reported diarrhoea and two reported abnormal urine odour.

In Study P903-20, TEAEs were reported by three (37.5%) subjects in the 1500 mg singled dose cohort, five (62.5%) in the 2000 mg single dose, six (75.0%) in the multiple dose and three (66.7%) in the placebo. Three subjects in the 2000 mg single dose cohort reported nausea. There were no clinically significant laboratory test abnormalities.

In Study P903-02 there were a total of 28 TEAEs reported in 13 (56.5%) subjects. Nausea, dizziness, headache, bradycardia and URTI were each reported in two subjects. There were no clinically significant, treatment emergent laboratory test abnormalities.

In Study P903-04, TEAEs were reported in seven (58.3%) subjects. The only TEAE reported in more than one subject was peripheral oedema (reported in two subjects). There were no clinically significant abnormalities in clinical laboratory tests.

In Study P903-18, there were four TEAEs in three subjects. There were no clinically significant, treatment emergent clinical laboratory test abnormalities.

In Study 903-11, TEAEs were reported in four (23.5%) subjects in the elderly group and one (6.3%) in the young. Three subjects reported headache. There were no clinically significant laboratory test abnormalities.

Study P903-15 there were eight TEAEs in five subjects. There was one SAE: pathological fracture of the right humerus in a subject with osteomyelitis. One subject did not receive the full dose of ceftaroline fosamil because of extravasation. One subject had a prolonged QTcB of 442 msec at baseline, 442 msec pre-dose, 444 msec at end of infusion and 446 msec on Day 2. One subject had APTT of 91.0 seconds on Day 2, compared with 40.0 seconds at baseline but had received plasma, red blood cells, albumin and platelets for blood loss from the trauma and subsequent surgery.

In Study P903-05, TEAEs were reported in 20 (37.0%) subjects in the ceftaroline arm, 19 (35.8%) in the moxifloxacin and eleven (20.4%) in the placebo. In the ceftaroline group eleven (20.4%) reported nausea, four (7.4%) vomiting, four (7.4%) contact dermatitis, three (5.6%) diarrhoea, three (5.6%) abdominal pain and three (5.6%) headache. There were no laboratory values that fell within the criteria for PCS.

Study P903-14, there were ten TEAEs reported in five subjects. The most commonly reported TEAE was nausea in two (16.7%) subjects. There were no SAEs, deaths or DAEs. There were no clinically significant abnormalities in clinical laboratory tests or ECGs.

7.4.2. Treatment-related adverse events (adverse drug reactions)[38]

7.4.2.1. Pivotal studies

7.4.2.1.1. Pivotal studies for cSSTI

In Study P903-03, there were 95 treatment related AEs reported in 23 (34.3%) subjects in the ceftaroline group and 57 in 13 (40.6%) in the comparator.

In Study P903-06, treatment related AEs were recorded in 99 (28.1%) subjects in the ceftaroline group and 99 (28.5%) in the comparator. Pruritus was more common in the comparator group than in the ceftaroline: 6.6% subjects compared with 2.6%.

In Study P903-07, AEs related to study drug were reported in 64 (18.8%) subjects in the ceftaroline group and 82 (24.2%) in the comparator. AEs related to study drug occurring in 3% or more of subjects in either treatment group were diarrhoea, 14 (4.1%) subjects in the ceftaroline group and ten (2.9%) in the comparator and pruritus seven (2.1%) subjects in the ceftaroline group and 23 (6.8%) in the comparator. Anaphylactic shock and anaphylactic reaction were each reported once in two separate subjects and were attributed to ceftaroline.

In Study P903-19, AEs related to study drug were reported in 45 (45.9%) of the ceftaroline group and 18 (40.0%) of the comparator. AEs related to study treatment with incidences differing by 3% or more between the study groups were nausea (11.2% in the ceftaroline and 15.6% in the comparator), vomiting (2.0% and 6.7%), injection site irritation (6.1% and 0%), injection site pain (3.1% and 0%), pyrexia (1.0% and 4.4%), headache (7.1% and 15.6%), dysgeusia (5.1% and 0%) and rash (3.1% and 0%).

7.4.2.1.2. Pivotal studies in CAP

In Study P903-08, AEs related to study drug were reported in 51 (17.1%) subjects in the ceftaroline group and 39 (12.7%) in the ceftriaxone. The most common study drug-related TEAEs in the ceftaroline group were diarrhoea (4.4% ceftaroline; 1.0% ceftriaxone), nausea (1.3% ceftaroline; 0.6% ceftriaxone) and phlebitis (1.3% ceftaroline; 0.6% ceftriaxone).

In Study P903-09, AEs related to treatment were reported in 39 (12.4%) subjects in the ceftaroline group and 42 (13.7%) in the ceftriaxone. The most common study drug-related AE was phlebitis, occurring in 2.9% subjects in the ceftaroline group and 1.6% in the ceftriaxone.

[38] Sponsor clarification: "Treatment related adverse events as assessed by the investigator."

7.4.3. Deaths and other serious adverse events

7.4.3.1. Pivotal studies

7.4.3.1.1. Pivotal studies in cSSTI

In Study P903-03, SAEs were reported in three (4.5%) subjects in the ceftaroline group (gangrene, skin infection and pulmonary oedema) and two (6.3%) in the comparator (infections and interstitial nephritis). There were no deaths reported during the study.

In Study P903-06, SAEs were reported in 16 (4.6%) subjects in the ceftaroline group and 12 (4.6%) in the comparator. There was no apparent pattern to the SAEs. Three (0.9%) subjects in the ceftaroline group died (respiratory failure, neck carcinoma and cardiopulmonary insufficiency), compared with none in the comparator. None of the deaths were attributed to ceftaroline or to cSSTI.

In Study P903-07, SAEs were reported in 14 (4.1%) subjects in the ceftaroline group and 16 (4.7%) in the comparator. Anaphylactic shock and anaphylactic reaction were each reported once in two separate subjects and were attributed to ceftaroline. There was no apparent pattern in the SAEs. There were no deaths reported during the study period. However, there were two deaths in each treatment group outside of the study period. The causes of death were: in the ceftaroline group multi-organ failure and myocardial infarction; and in the comparator chronic lymphocytic leukaemia and myocardial infarction/ arrhythmia/ pulmonary embolism.

In Study P903-19, SAEs were reported in four (4.1%) subjects in the ceftaroline group (cellulitis, necrotizing fasciitis, postoperative wound infection and skin infection) and none in the comparator. No deaths were reported during the study.

7.4.3.1.2. Pivotal studies in CAP

In Study P903-08, SAEs were reported in 28 (9.4%) subjects in the ceftaroline group and 33 (10.7%) in the ceftriaxone. Neoplasms were more common with the ceftaroline group, five (1.7%) subjects compared with one (0.3%) in the ceftriaxone but none were considered to be related to treatment. Death was reported for six (2.0%) subjects in the ceftaroline group and six (1.9%) in the ceftriaxone. There was no apparent pattern to the deaths in the ceftaroline group.

In Study P903-09, SAEs were reported in 41 (13.0%) subjects in the ceftaroline group and 39 (12.7%) in the ceftriaxone. There was no apparent pattern to the SAEs. Death occurred for nine (2.9%) subjects in the ceftaroline group and six (2.0%) in the ceftriaxone. There was no apparent pattern in the TEAEs with an outcome of death.

7.4.3.1.3. Other studies

Study P903-15 there was one SAE: pathological fracture of the right humerus in a subject with osteomyelitis.

There were no deaths or SAEs in Study CXL-PK-01, Study P903-13, Study P903-01, Study P903-17, Study P903-20, Study P903-02, Study P903-04, Study P903-18, Study 903-11, Study P903-05 or Study P903-14. There were no deaths reported in Study P903-15.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal studies

7.4.4.1.1. Pivotal studies in cSSTI

In Study P903-03, DAE was reported for three (4.5%) subjects in the ceftaroline group (mononucleotide syndrome, prolonged QTC > 500 ms and gangrene of toe) and one (3.1%) in the comparator (skin rash and fever).

In Study P903-06, DAE was recorded for 13 (3.7%) subjects in the ceftaroline group and 16 (4.6%) in the comparator. There was no apparent pattern to the AEs leading to discontinuation (Table 18).

Table 18. Adverse Events Leading to Premature Discontinuation of Study Drug Therapy, MITT Population. Table continued across 2 pages.

System Organ Class *Preferred Term*[a]	*Ceftaroline* *(N = 351)* *n (%)*	*Vancomycin plus Aztreonam* *(N = 347)* *n (%)*
Subjects with at least one AE leading to discontinuation of study drug[b]	13 (3.7)	16 (4.6)
Cardiac disorders	0	1 (0.3)
Cardiac failure congestive	0	1 (0.3)
Eye disorders	0	1 (0.3)
Eye swelling	0	1 (0.3)
Gastrointestinal disorders	0	1 (0.3)
Gingival swelling	0	1 (0.3)
General disorders and administration site conditions	1 (0.3)	2 (0.6)
Chest pain	1 (0.3)	0
Infusion site urticaria	0	1 (0.3)
Pyrexia	0	1 (0.3)
Immune system disorders	3 (0.9)	3 (0.9)
Hypersensitivity	2 (0.6)	3 (0.9)
Anaphylactic reaction	1 (0.3)	0
Infections and infestations	2 (0.6)	4 (1.2)
Cellulitis	1 (0.3)	0
Clostridial infection	1 (0.3)	0
Clostridium difficile colitis	0	1 (0.3)
Osteomyelitis	0	1 (0.3)
Viral infection	0	1 (0.3)
Wound infection	0	1 (0.3)
Investigations	1 (0.3)	1 (0.3)
Blood creatinine increased	1 (0.3)	0
Blood urea increased	1 (0.3)	0
Laboratory test abnormal[c]	0	1 (0.3)
Metabolism and nutrition disorders	0	1 (0.3)
Dehydration	0	1 (0.3)

Table 18 continued. Adverse Events Leading to Premature Discontinuation of Study Drug Therapy, MITT Population.

System Organ Class *Preferred Term*[a]	*Ceftaroline* *(N = 351)* *n (%)*	*Vancomycin plus Aztreonam* *(N = 347)* *n (%)*
Skin and subcutaneous tissue disorders	6 (1.7)	8 (2.3)
Pruritus generalized	2 (0.6)	1 (0.3)
Rash generalized	2 (0.6)	1 (0.3)
Rash maculo-papular	2 (0.6)	0
Dermatitis allergic	1 (0.3)	2 (0.6)
Urticaria	1 (0.3)	0
Pruritus	0	2 (0.6)
Rash	0	2 (0.6)
Urticaria generalized	0	1 (0.3)
Vascular disorders	0	2 (0.6)
Hypotension	0	1 (0.3)
Thrombophlebitis	0	1 (0.3)

Abbreviations: MITT = modified intent to treat.

a MedDRA Version 9.1 was used to code adverse events. Subjects were counted once within each preferred term.

b Subject 0002-06061 in the vancomycin plus aztreonam group discontinued outpatient study drug therapy prematurely due to insufficient therapeutic effect. The subject was hospitalized to receive IV antibiotic therapy and thus, a serious adverse event of wound infection was reported. The subject appears on this table as a discontinuation of study drug due to a wound infection.

c Subject 6506-06252 had elevated vancomycin levels, which persisted despite decrease of vancomycin doses, noted by the unblinded Pharmacist who, to maintain the blind, recommended discontinuation of therapy due to a "lab value out of range."

In Study P903-07, DAEs were reported in eight (2.3%) subjects in the ceftaroline group and 17 (5.0%) in the comparator. Although there were more DAEs in the comparator group, it is notable that in the ceftaroline group one subjects discontinued because of anaphylactic reaction and one because of anaphylactic shock.

In Study P903-19, DAE was reported in four (4.1%) subjects in the ceftaroline group (necrotizing fasciitis, postoperative wound infection, maculo-papular rash and rash) and none in the comparator.

7.4.4.1.2. Pivotal studies in CAP

In Study P903-08, DAE was reported for 11 (3.7%) subjects in the ceftaroline group and 12 (3.9%) in the ceftriaxone. There was no apparent pattern to the DAEs.

In Study P903-09, DAE was reported in 16 (5.1%) subjects in the ceftaroline group and 13 (4.2%) in the ceftriaxone. There was no apparent pattern to the DAEs.

7.4.4.2. Other studies

In Study CXL-PK-01, two subjects withdrew because of TEAEs, both treated with ceftaroline 600 mg: generalised rash on Day 8; and generalised rash, pruritus, diaphoresis, fever and tachycardia on Day 9.

In Study P903-20, four (50%) subjects treated with ceftaroline fosamil in the multiple dose cohort discontinued: urticaria, rash maculopapular, phlebitis and pruritus.

In Study P903-05 there was one DAE during the placebo arm: neutropenia that did not fall within the criteria for PCS.

There were no DAEs in Study P903-13, Study P903-01, Study P903-17, Study P903-02, Study P903-04, Study P903-18, Study 903-11 or Study P903-14.

7.5. Laboratory tests

7.5.1. Pivotal studies

In Study P903-03, there were no trends demonstrated in mean values for clinical laboratory tests. However, a positive direct Coomb's test was recorded for five (13.2%) subjects in the ceftaroline group at EOT and for none in the comparator. There were no apparent patterns in the clinical chemistry results. At EOT, shift from normal to above normal aspartate aminotransferase (AST) occurred in nine (17.6%) subjects in the ceftaroline group and six (28.6%) in the comparator.

In Study P903-06, there was a positive direct Coombs test in 20 (6.5%) subjects in the ceftaroline group and none in the comparator. There was no clinical or laboratory evidence of haemolytic anaemia. Five (1.6%) subjects in the both treatment groups had prolongation of the PT. There were no other apparent differences between the treatment groups in haematology parameters. There was no apparent pattern for abnormalities in clinical chemistry. Alanine aminotransferase (ALT) was elevated in six (1.7%) subjects in the ceftaroline group and eight (2.4%) in the comparator. AST was elevated in five (1.4%) subjects in the ceftaroline group and five (1.5%) in the comparator.

In Study P903-07, a positive direct Coombs test was reported in 49 (17.2%) subjects in the ceftaroline group and 25 (8.8%) in the comparator. Prothrombin time was elevated in four (1.3%) subjects in the ceftaroline group and three (1.0%) in the comparator. Elevated ALT was reported in two (0.6%) subjects in the ceftaroline group and nine (2.7%) in the comparator. Elevated AST was reported in four (1.2%) subjects in the ceftaroline group and nine (2.7%) in the comparator.

In Study P903-19 a positive direct Coombs test was reported for 19 (21.1%) subjects in the ceftaroline group and two (4.5%) in the comparator. Other than this, there was no apparent pattern to the abnormalities in haematology test results. There were no abnormalities in coagulation parameters. One subject in the ceftaroline group had a potentially clinically significant increase in ALT and AST.

In Study P903-08, a positive direct Coombs test was reported in 28 (11.8%) subjects in the ceftaroline group and 14 (5.2%) in the ceftriaxone but there was no difference between the groups in the number of subjects with low haematocrit. There were no abnormalities in post-baseline coagulation parameters. Elevated ALT was reported in six (2.2%) subjects in the ceftaroline group and ten (3.5%) in the ceftriaxone. Elevated AST was reported in two (0.7%) subjects in the ceftaroline group and eight (2.9%) in the ceftriaxone.

In Study P903-09, a positive direct Coombs test was reported in 23 (8.1%) subjects in the ceftaroline group and ten (3.8%) in the ceftriaxone. Two (0.8%) subjects in the ceftaroline group but none in the ceftriaxone had a significant decrease in haematocrit and haemoglobin concentration. There were no abnormalities in coagulation parameters. Clinically significant elevation in ALT was observed in seven (2.5%) subjects in the ceftaroline group and eight (3.1%) in the ceftriaxone. Clinically significant elevation in AST was observed in four (1.5%) subjects in the ceftaroline group and five (2.0%) in the ceftriaxone.

7.6. Postmarketing experience

A Risk Management Plan was included in the submission.

7.7. Evaluator's overall conclusions on clinical safety

TEAEs were reported in around 60% of subjects and occurred at a similar rate to comparator treatment. Headache occurred in up to 16% of subjects, nausea 12% and diarrhoea 5%.

In the Phase I studies, the rates of TEAEs increased with dose and the level of tolerability appeared to be 600 mg q12h.

Urine discolouration and odour occurred at the 600 mg q12h dosing level. Some subjects reported body odour. Injection site AEs (pain/discomfort/thrombophlebitis) occurred in approximately 40% of subjects.

Ceftaroline did not appear to be associated with QT prolongation in either the thorough QT study or in the other clinical studies.

Ceftaroline did not appear to be associated with seizures or hepatobiliary dysfunction.

SAEs were uncommon and were not usually attributable to the study treatment. In Study P903-07, anaphylactic shock and anaphylactic reaction were each reported once in two subjects and were attributed to ceftaroline.

Death was uncommon and none were attributed to study treatment.

Ceftaroline appeared to be well tolerated with up to 5% of subjects discontinuing because of AEs that were not usually attributed to study treatment.

Up to 21% of subjects developed a positive direct Coomb's test during the course of treatment. However, this did not translate to an increased incidence of haemolytic anaemia.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

For the two indications sought in the present application ceftaroline had comparable efficacy to an acceptable standard of care for Australia. In subjects with cSSTI non-inferiority was demonstrated in comparison with vancomycin and in subjects with CAP non-inferiority was demonstrated in comparison with ceftriaxone. Efficacy was demonstrated for the intravenous route of administration at the dose level proposed for marketing.

Efficacy was demonstrated for conditions where there is a clinical need for new treatments. Ceftaroline had good efficacy against MRSA and also penicillin resistant strains of Streptococcus pneumoniae.

Although the comparators used in the efficacy studies would not normally be first line treatment for cSSTI or CAP in Australia the comparators do provide an acceptable standard of care for these conditions. Vancomycin would be used as a second line agent for cSSTI and first-line for patients with penicillin allergy and linezolid would normally be reserved as a third line agent. Aztreonam is not usually used for the indication of cSSTI in Australia but is acceptable treatment for cSSTI resulting from Gram negative organisms. Ceftriaxone would not normally be first line treatment for CAP in Australia but would be an acceptable treatment for this indication and is commonly used for hospital acquired pneumonia in the Australian setting.

8.2. First round assessment of risks

Ceftaroline demonstrated an acceptable safety profile for an antibiotic in the Australian setting. TEAEs were reported in around 60% of subjects and occurred at a similar rate to comparator treatment. Headache occurred in up to 16% of subjects, nausea 12% and diarrhoea 5%. The rates of TEAEs increased with dose and the level of tolerability appeared to be 600 mg q12h.

Urine discolouration and odour occurred at the 600 mg q12h dosing level. Some subjects reported body odour. Injection site AEs (pain/discomfort/thrombophlebitis) occurred in up to 40% of subjects.

Ceftaroline did not appear to be associated with QT prolongation in either the thorough QT study or in the other clinical studies. Ceftaroline did not appear to be associated with seizures or hepatobiliary dysfunction.

SAEs were uncommon and were not usually attributable to the study treatment. Anaphylactic shock and anaphylactic reaction were each reported once in two separate subjects and were attributed to ceftaroline.

Death was uncommon and none were attributed to study treatment.

Ceftaroline appeared to be well tolerated with up to 5% of subjects discontinuing because of AEs but these were not usually attributed to study treatment.

Up to 21% of subjects developed a positive direct Coomb's test during the course of treatment. However, this did not translate to an increased incidence of haemolytic anaemia.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of ceftaroline, given the proposed usage, was considered to be favourable.

9. First round recommendation regarding authorisation

The following indication for ceftaroline fosamil (Zinforo) should be approved:

> *Zinforo is indicated for the treatment of the following infections in adults from the age of 18 years:*
>
> - *Complicated skin and soft tissue infections*
> - *Community-acquired pneumonia*

Therapeutic Goods Administration

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