Clinical Study Report Synopsis

Drug Substance Ceftaroline fosamil

Study Code D3720C00010

Edition Number 1

EudraCT Number 2011-000409-27

A Phase I, Single Centre, Randomised, Double-blind, Placebo-controlled Parallel Group Study to Assess the Safety, Tolerability, and Pharmacokinetics of Ceftaroline after Different Intravenous Dose Regimens of Ceftaroline Fosamil to Healthy Subjects

Study dates: First subject enrolled: 12 July 2012
Last subject last visit: 16 November 2012

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of single and multiple intravenous infusions of different dose regimens of ceftaroline fosamil as compared to placebo in healthy male and female subjects	Adverse events, local tolerability, laboratory variables, vital signs, electrocardiogram, and physical examination
Secondary	Pharmacokinetic	To characterise the PK of ceftaroline, ceftaroline fosamil (the prodrug of ceftaroline), and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) in plasma and urine following single- and multiple-dose administrations of different ceftaroline fosamil intravenous infusion regimens in healthy male and female subjects	Single dose on Day 1: C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, $AUC_{(0-12)}$, $AUC_{(0-8)}$, λ_z, $t_{1/2\lambda z}$, $R_{M/D,Cmax}$, $R_{M/D,AUC}$, $R_{M/D,AUC(0-t)}$, MRT, CL/F, V_z/F, or V_{ss}/F, A_e, f_e, $f_{e,total}$, CL_R. (A_e, f_e, $f_{e,total}$ calculated for each interval, cumulatively, and overall during the 24-hours interval) Multiple dose Days 4 to 8: $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, $t_{ss,min}$, $AUC_{(0-t)}$, AUC_τ, $C_{ss,av}$, FI, $R_{M/D,Cmax}$, $R_{M/D,AUC\tau}$, λ_z, $t_{1/2\lambda z}$, $R_{ac(Cmax)}$, $R_{ac(AUC)}$, linearity factor, MRT, CL_{ss}/F, V_z/F, V_{ss}/F Day 8: $A_{e,ss}$, $f_{e,ss}$, $f_{e,ss,total}$, $CL_{R,ss}$ (calculated for each interval, cumulatively, and overall during the dosing interval)
Exploratory[a]	Biomarkers	To collect and store blood samples for potential future exploratory research aimed at exploring biomarkers involved in the PK, pharmacodynamics, safety, tolerability, and efficacy of ceftaroline fosamil	-

[a] If performed, these results will be reported separately from this Clinical Study Report in a stand-alone report.

A_e: amount of analyte excreted in the urine; $A_{e,ss}$: amount of analyte excreted in the urine at steady state;
AUC: area under the plasma concentration-time curve; $AUC_{(0-8)}$: AUC from zero to 8 hours after the start of the

infusion; $AUC_{(0-12)}$: AUC from zero to 12 hours after the start of the infusion; $AUC_{(0-t)}$: AUC from zero to the time of the last quantifiable concentration; AUC_{τ}: AUC from zero to the end of the dosing interval; CL/F: apparent body clearance of drug from plasma; CL_R: renal clearance; $CL_{R,ss}$: renal clearance at steady state; CL_{ss}/F: apparent total body clearance of drug from plasma at steady state; C_{max}: maximum plasma concentration; $C_{ss,av}$: average plasma concentration during the dosing interval; $C_{ss,max}$: maximum plasma concentration at steady state; $C_{ss,min}$: minimum plasma concentration at steady state; f_e: fraction of dose excreted in the urine; $f_{e,ss}$: fraction of dose excreted in the urine at steady state; $f_{e,ss,total}$: total fraction of dose excreted in the urine at steady state; $f_{e,total}$: total fraction of dose excreted in the urine; FI: fluctuation index; λ_z: apparent terminal rate constant; MRT: mean residence time; PK: pharmacokinetic(s); $R_{ac(AUC)}$: accumulation ratio based on AUC; $R_{ac(Cmax)}$: accumulation ratio based on C_{max}; $R_{M/D,AUC}$: metabolite/parent AUC ratio; $R_{M/D,AUC(0-t)}$: metabolite/parent $AUC_{(0-t)}$ ratio; $R_{M/D,AUC\tau}$: metabolite/parent AUC_{τ} ratio; $R_{M/D,Cmax}$: metabolite/parent C_{max} ratio; $t_{1/2\lambda z}$: terminal half-life; t_{max}: time to maximum plasma concentration; $t_{ss,max}$: time to maximum plasma concentration at steady state; $t_{ss,min}$: time to minimum plasma concentration at steady state; V_{ss}/F: apparent volume of distribution at steady state; V_z/F: apparent volume of distribution based on the terminal phase.

Study design

This was a Phase I, randomised, double-blind, placebo-controlled, parallel group study in healthy male volunteers conducted at a single study centre in 2 cohorts. The ceftaroline fosamil doses administered were 600 mg every 12 hours (infused over 1 hour) in Cohort 1 and 600 mg every 8 hours (infused over 2 hours) in Cohort 2. After a screening period of up to 28 days, the healthy volunteers were admitted to the study centre on Day -1, discharged on Day 9, and followed up 7 to 10 days after discharge.

On Days 1 and 8, the healthy volunteers received a single dose of 600 mg ceftaroline fosamil or placebo. Repeated infusions commenced on Day 2. The healthy volunteers then received ceftaroline fosamil or placebo every 12 hours (Cohort 1) or every 8 hours (Cohort 2) from Days 2 to 7.

Target subject population and sample size

Up to 40 healthy volunteers aged 18 to 55 years (inclusive) were to participate in 2 cohorts. Each cohort was divided into 4 subgroups of 5 healthy volunteers each. Twenty healthy volunteers were to participate in each cohort and were to receive either ceftaroline fosamil (15 healthy volunteers) or placebo (5 healthy volunteers).

Screened: 88 healthy volunteers

Planned: 40 healthy volunteers

Randomised: 41 healthy volunteers

Analysed: 41 healthy volunteers

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Details of the investigational product(s)

Investigational product	Dosage form and strength	Manufacturer	Batch number
Ceftaroline fosamil	30 mg/mL intravenous infusion (600 mg)	FACTA Pharmaceutical S.p.A	206245/01 206245/02
Placebo	0.9% sodium chloride	AstraZeneca	1201577 1201183

Duration of treatment

Single dose on Days 1 and 8, multiple doses on Days 2 to 7

Statistical methods

Due to the exploratory nature of the study, the sample size was not based on formal statistical considerations.

No formal statistical hypothesis testing was performed. The safety and tolerability data were summarised using descriptive statistics, frequency counts or graphically, as appropriate.

The safety and tolerability data were summarised using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum) by treatment group (continuous variables) and in frequency tables (frequency and proportion) by treatment group (categorical variables).

The pharmacokinetics (PK) of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 was evaluated by assessment of concentrations in plasma and urine and calculation of PK parameters. Pharmacokinetic data were summarised descriptively including tables, listings, and graphs, as appropriate. Time to steady state was evaluated by graphical assessments.

Subject population

Of the 41 healthy volunteers (100.0%) who were randomised, 39 healthy volunteers (95.1%) completed the treatment and the study. One healthy volunteer (2.4%) in Cohort 1 (ceftaroline fosamil) prematurely withdrew consent and 1 healthy volunteer (2.4%) in Cohort 2 (placebo) was prematurely withdrawn due to an adverse event (AE).

The age of the healthy volunteers ranged from 19 to 51 years (mean 30 years) and the body mass index (BMI) from 20 to 30 kg/m^2 (mean 24 kg/m^2), in accordance with the inclusion criteria. All healthy volunteers were male with a minimum weight of 58 kg.

The demographic and baseline characteristics of the healthy volunteers were considered representative of the target population for this study, despite no female enrolment due to number of cannulae required and lack of adequate venous access.

Summary of pharmacokinetic results

Plasma pharmacokinetics

Ceftaroline

Ceftaroline single-dose and multiple-dose pharmacokinetic parameters are summarised in Table S3 and Table S4, respectively.

Table S3 Summary of ceftaroline plasma pharmacokinetic parameters on single-dose Day 1 [geometric means (%CV)] (pharmacokinetic analysis set)

Parameters (units)	Cohort 1 (600 mg, 1-h, q12h) n = 16	Cohort 2 (600 mg, 2-h, q8h) n = 15
AUC (µg·h/mL)	66.8 (15.2%)	63.7 (24%)
$AUC_{(0-t)}$ (µg·h/mL)	66.3 (15.4%)	63.3 (24.2%)
C_{max} (µg/mL)	26.2 (11.4%)	19.2 (21.3%)
t_{max} (h) [a]	0.92 (0.92 - 1.10)	1.92 (1.92 - 1.92)
$t_{1/2\lambda z}$ (h)	2.46 (13.2%)	2.53 (12.4%)
CL/F (L/h)	7.93 (15.1%)	8.33 (24%)
V_z/F (L)	28.2 (15.6%)	30.4 (18%)
V_{ss}/F (L)	23.2 (11.8%)	28.8 (16.5%)
$R_{M/D,Cmax}$ [b]	9.52 (19%)	14.6 (26.3%)
$R_{M/D,AUC(0-t)}$ [b]	31.7 (23.2%)	31.6 (33.5%)

Notes:
IV intravenous; q8h every 8 hours; q12h every 12 hours.
Cohort 1: 600 mg ceftaroline fosamil 1-hour IV infusion q12h
Cohort 2: 600 mg ceftaroline fosamil 2-hour IV infusion q8h
[a] t_{max}: median (range) presented.
[b] Exposure ratios of ceftaroline/ceftaroline fosamil, adjusted for molecular weight differences.

Table S4 Summary of ceftaroline plasma pharmacokinetic parameters on multiple-dose Day 4 and Day 8 [geometric means (%CV)] (pharmacokinetic analysis set)

Parameters (units)	Multiple-dose Day 4		Multiple-dose Day 8	
	Cohort 1 (600 mg, 1-h, q12h) n = 15	Cohort 2 (600 mg, 2-h, q8h) n = 15	Cohort 1 (600 mg, 1-h, q12h) n = 15	Cohort 2 (600 mg, 2-h, q8h) n = 15
AUC_{τ} (µg·h/mL)	66.4 (16%)	64.2 (22.5%)	67.6 (17%)	65.1 (22%)
$C_{ss,max}$ (µg/mL)	26.6 (11.9%)	20.3 (20.2%)	26.5 (15%)	20.5 (17.7%)
$t_{ss,max}$ (h)[a]	0.93 (0.92 - 1.08)	1.92 (1.50 - 2.08)	0.92 (0.92 - 1.08)	1.92 (1.92 - 2.08)
$C_{ss,min}$ (µg/mL)	0.409 (39.6%)	1.66 (44.3%)	0.401 (38%)	1.71 (42.2%)
$C_{ss,av}$	5.59 (16%)	8.11 (22.5%)	5.63 (17%)	8.13 (21.9%)
FI (%)	467 (8.2%)	229 (11.5%)	464 (7.1%)	230 (9.3%)
$t_{1/2,\lambda z}$ (h)	2.28 (10.1%)	1.95 (10.6%)[b]	2.63 (10.1%)	2.73 (12.2%)
CL_{ss}/F (L/h)	7.99 (16%)	8.25 (22.5%)	7.85 (17.1%)	8.14 (22%)
V_{ss}/F (L)	26.2 (13.1%)	23.2 (15.2%)[b]	29.7 (12.4%)	32.1 (17.4%)
$R_{M/D,Cmax}$ [c]	9.39 (23.6%)	15.6 (31.8%)	9.54 (21.8%)	16 (37.6%)
$R_{M/D,AUC\tau}$ [c]	31.9 (26.3%)	32.5 (32.2%)	32 (26.3%)	33.5 (36.2%)
$R_{ac(Cmax)}$	1.02 (7.0%)	1.06 (11.1%)	1.01 (6.4%)	1.07 (7.1%)
$R_{ac(AUC)}$	1.02 (4.3%)	1.10 (6.4%)	1.04 (4.8%)	1.12 (6.6%)
Linearity Factor	0.996 (4.4%)	1.01 (6.4%)	1.01 (4.6%)	1.02 (7.1%)

Notes:
IV intravenous; q8h every 8 hours; q12h every 12 hours.
Cohort 1: 600 mg ceftaroline fosamil 1-hour IV infusion q12h
Cohort 2: 600 mg ceftaroline fosamil 2-hour IV infusion q8h
[a] $t_{ss,max}$: median (range) presented.
[b] n = 14
[c] Exposure ratios of ceftaroline/ceftaroline fosamil, adjusted for molecular weight differences.

Across study days in both cohorts, ceftaroline peak exposure (C_{max} on Day 1, $C_{ss,max}$ on Days 4 and 8) and total exposures ($AUC_{(0-t)}$ on Day 1, AUC_{τ} on Days 4 and 8) were approximately 9- to 16-fold, and 32-to 33-fold, respectively, ceftaroline fosamil exposures. Ceftaroline PK was demonstrated to be time-independent. Consistent with the short $t_{1/2,\lambda z}$ of approximately 2.5 hours, no appreciable ceftaroline accumulation in peak and total exposures were observed after multiple ceftaroline fosamil infusions q12h (Cohort 1) or q8h (Cohort 2).

In comparison to the 600-mg 1-h infusion q12h regimen in Cohort 1, when the same dose of ceftaroline fosamil was administered as 2-h infusion q8h in Cohort 2, ceftaroline $C_{ss,max}$ was

approximately 25% lower, $C_{ss,min}$ and $C_{ss,av}$ were higher with lower fluctuations in plasma concentrations due to prolonged infusion and more frequent dosing. At the end of the respective dosing interval, Cohort 2 geometric mean $C_{ss,min}$ were slightly higher, 1.66 µg/mL (Day 4) and 1.71 µg/mL (Day 8) compared to 0.409 µg/mL (Day 4) and 0.401 µg/mL (Day 8) in Cohort 1.

Ceftaroline fosamil

Ceftaroline fosamil single-dose and multiple-dose pharmacokinetic parameters are summarised in Table S5 and Table S6, respectively.

Table S5 Summary of ceftaroline fosamil plasma pharmacokinetic parameters on single-dose Day 1 [geometric means (%CV)] (pharmacokinetic analysis set)

Parameters (units)	Cohort 1 (600 mg, 1-h, q12h) n = 16	Cohort 2 (600 mg, 2-h, q8h) n = 15
$AUC_{(0-t)}$ (µg·h/mL)	2.37 (23.4%)	2.26 (25%)
C_{max} (µg/mL)	3.12 (20.8%)	1.49 (27.3%)
t_{max} (h) [a]	0.67 (0.17 - 1.08)	1.50 (0.50 - 1.92)

Notes:
IV intravenous; q8h every 8 hours; q12h every 12 hours.
Cohort 1: 600 mg ceftaroline fosamil 1-hour IV infusion q12h
Cohort 2: 600 mg ceftaroline fosamil 2-hour IV infusion q8h
[a] t_{max}: median (range) presented.

Table S6 Summary of ceftaroline fosamil plasma pharmacokinetic parameters on multiple-dose Day 4 and Day 8 [geometric means (%CV)] (pharmacokinetic analysis set)

Parameters (units)	Multiple-dose Day 4		Multiple-dose Day 8	
	Cohort 1 (600 mg, 1-h, q12h) n = 15	Cohort 2 (600 mg, 2-h, q8h) n = 15	Cohort 1 (600 mg, 1-h, q12h) n = 15	Cohort 2 (600 mg, 2-h, q8h) n = 15
AUC_{τ} (µg·h/mL)	2.36 (29.2%)	2.23 (28.4%)	2.39 (25.9%)	2.20 (31.3%)
$C_{ss,max}$ (µg/mL)	3.21 (26.3%)	1.47 (27.1%)	3.15 (23.1%)	1.45 (36.4%)
$t_{ss,max}$ (h)[a]	0.92 (0.33 - 0.97)	1.00 (0.50 - 1.92)	0.33 (0.33 - 0.92)	1.50 (0.50 - 1.93)
$C_{ss,min}$ (µg/mL)[b]	ND	ND	ND	ND
$C_{ss,av}$	0.198 (29.4%)	0.282 (28.5%)	0.199 (26%)	0.275 (31.2%)
FI (%)	1620 (9.3%)	522 (4.4%)	1580 (9%)	529 (8.6%)
$R_{ac(Cmax)}$	1.01 (23.8)	0.991 (23.7%)	0.994 (16.3%)	0.978 (39.3%)

Notes:
IV intravenous; ND not determined; q8h every 8 hours; q12h every 12 hours.
Cohort 1: 600 mg ceftaroline fosamil 1-hour IV infusion q12h
Cohort 2: 600 mg ceftaroline fosamil 2-hour IV infusion q8h
[a] $t_{ss,max}$: median (range) presented.
[b] Geometric mean not estimable; all concentrations were BLQ and set to 0 in the PK analysis.

Ceftaroline fosamil concentrations rapidly decreased after the infusions stopped. Across all study days in both cohorts, no quantifiable concentrations were measured in any samples collected 1 hour after the end of the infusion. Thus, no ceftaroline fosamil accumulation was observed following q12h (Cohort 1) or q8h (Cohort 2) multiple-dose administration.

Ceftaroline M-1

Ceftaroline M-1 single-dose and multiple-dose pharmacokinetic parameters are summarised in Table S7 and Table S8.

Table S7 Summary of ceftaroline M-1 plasma pharmacokinetic parameters on single-dose Day 1 [geometric means (%CV)] (pharmacokinetic analysis set)

Parameters (units)	Cohort 1 (600 mg, 1-h, q12h) n = 16	Cohort 2 (600 mg, 2-h, q8h) n = 15
AUC (µg·h/mL)	10.8 (17.9%)	13.3 (25.4%)
C_{max} (µg/mL)	1.09 (16%)	1.28 (22.8%)
t_{max} (h) [a]	3.03 (3.00 - 4.00)	4.00 (2.08 - 6.00)
$t_{1/2\lambda z}$ (h)	4.44 (14.8%)	4.29 (8.8%)
$R_{M/D,Cmax}$ [b]	0.0403 (12.3%)	0.065 (24.2%)
$R_{M/D,AUC}$ [b]	0.158 (14.3%)	0.202 (25%)

Notes:
IV intravenous; q8h every 8 hours; q12h every 12 hours.
Cohort 1: 600 mg ceftaroline fosamil 1-hour IV infusion q12h
Cohort 2: 600 mg ceftaroline fosamil 2-hour IV infusion q8h
[a] t_{max}: median (range) presented.
[b] Exposure ratios of ceftaroline M-1/ceftaroline adjusted for molecular weight differences.

Table S8 Summary of ceftaroline M-1 plasma pharmacokinetic parameters on multiple-dose Day 4 and Day 8 [geometric means (%CV)] (pharmacokinetic analysis set)

Parameters (units)	Multiple-dose Day 4		Multiple-dose Day 8	
	Cohort 1 (600 mg, 1-h, q12h) n = 15	Cohort 2 (600 mg, 2-h, q8h) n = 15	Cohort 1 (600 mg, 1-h, q12h) n = 15	Cohort 2 (600 mg, 2-h, q8h) n = 15
AUC_{τ} (µg·h/mL)	10.8 (14.8%)	12.4 (24.7%)	11.3 (18.9%)	13.1 (26.1%)
$C_{ss,max}$ (µg/mL)	1.32 (13.3%)	1.98 (21.9%)	1.34 (16.4%)	1.98 (22.9%)
$t_{ss,max}$ (h)[a]	3.00 (1.50 - 4.00)	2.25 (1.50 - 4.00)	3.00 (1.08 - 8.00)	2.25 (2.08 - 4.00)
$C_{ss,min}$ (µg/mL)	0.417 (21.1%)	1.15 (30.8%)	0.433 (22.2%)	1.21 (31.2%)
$C_{ss,av}$	0.913 (14.7%)	1.57 (24.6%)	0.94 (18.9%)	1.63 (26%)
FI (%)	97.7 (12.8%)	50.8 (31.3%)	96 (12.4%)	46.3 (23.3%)
$t_{1/2\lambda z}$ (h)	4.55 (13.9%)	ND	5.37 (8%)	5.42 (11.8%)
$R_{M/D,Cmax}$ [b]	0.0481 (12.9%)	0.0946 (16.9%)	0.0492 (13.7%)	0.0937 (19.6%)
$R_{M/D,AUC\tau}$ [b]	0.159 (14.9%)	0.188 (21.8%)	0.162 (17.9%)	0.195 (23.4%)
$R_{ac(Cmax)}$	1.21 (6.6%)	1.54 (15.5%)	1.24 (7.2%)	1.54 (9.8%)
$R_{ac(AUC)}$	1.24 (5.9%)	1.60 (10.0%)	1.30 (6.5%)	1.68 (8.6%)
Linearity Factor	0.994 (4.7%)	0.937 (6.4%)	1.04 (6.1%)	0.984 (5.6%)

Notes:
IV intravenous; ND not determined; q8h every 8 hours; q12h every 12 hours.
Cohort 1: 600 mg ceftaroline fosamil 1-hour IV infusion q12h
Cohort 2: 600 mg ceftaroline fosamil 2-hour IV infusion q8h
[a] $t_{ss,max}$: median (range) presented.
[b] Exposure ratios of ceftaroline M-1/ceftaroline adjusted for molecular weight differences.

Ceftaroline M-1 peak exposure (C_{max} on Day 1, $C_{ss,max}$ on Days 4 and 8) and total exposures (AUC on Day 1, AUC_{τ} on Days 4 and 8) were ≤20% the corresponding ceftaroline exposures, suggesting that ceftaroline M-1 is a minor metabolite of ceftaroline. Ceftaroline M-1 pharmacokinetics was also time-independent. Some accumulations were observed in the multiple-dose phase. Following repeated dosing q12h in Cohort 1 and q8h in Cohort 2 starting on Day 2, accumulations in peak and total exposures on Day 4 and Day 8 were approximately 20% to 30% and 50% to 70% for the respective cohorts.

Urine pharmacokinetics

The overall amounts and fractions of ceftaroline fosamil dose recovered in the urine over 24 hours on single-dose Day 1 or dosing intervals on multiple-dose Day 8, and CL_R are summarised in Table S9.

Table S9 Summary of urinary recoveries and CL_R on single-dose Day 1 and multiple-dose Day 8 [geometric means (%CV)] (pharmacokinetic analysis set)

Study day	Parameters (units)	Ceftaroline[a]		Ceftaroline M-1[a]	
		Cohort 1 (600 mg, 1-h, q12h)[b]	Cohort 2 (600 mg, 2-h, q8h)[c]	Cohort 1 (600 mg, 1-h, q12h)[c]	Cohort 2 (600 mg, 2-h, q8h)[c]
Day 1	$A_{e\,(0\text{-}24)}$ (mg)	351 (7.5%)	320 (28.4%)	41.2 (18.5%)	43.0 (15.2%)
	$f_{e\,(0\text{-}24)}$ (%)[d]	66.2 (7.5%)	60.4 (28.3%)	7.54 (18.6%)	7.87 (15.1%)
	CL_R (L/h)	5.29 (15.2%)	5.07 (21.3%)	4.00 (18.6%)	3.36 (23.9%)
Day 8	$A_{e\,(0\text{-}\tau)}$ (mg)	343 (12.6%)	348 (19.0%)	42.3 (19.2%)	48.3 (22.6%)
	$f_{e\,(0\text{-}\tau)}$ (%)[d]	64.7 (12.6%)	65.6 (19.0%)	7.75 (19.2%)	8.83 (22.5%)
	CL_R (L/h)	5.07 (19.7%)	5.34 (15.4%)	3.75 (17.8%)	3.70 (25.7%)

Notes:
IV intravenous; q8h every 8 hours; q12h every 12 hours.
Cohort 1: 600 mg ceftaroline fosamil 1-hour IV infusion q12h
Cohort 2: 600 mg ceftaroline fosamil 2-hour IV infusion q8h

[a] No quantifiable ceftaroline fosamil concentrations were measured in any of the urine samples.
[b] n = 16
[c] n = 15
[d] Adjusted for differences in molecular weights of ceftaroline or ceftaroline M-1 relative to ceftaroline fosamil.

The majority of the ceftaroline fosamil dose, approximately 60% to 66%, was recovered in the urine as ceftaroline. A much smaller fraction, approximately 7% to 9%, was recovered as ceftaroline M-1 and no renal excretion of ceftaroline fosamil was observed (ceftaroline fosamil was not quantifiable in any of the urine samples). CL_R accounted for the majority of ceftaroline CL/F (approximately 5 L/h vs. 8 L/h, respectively). In both cohorts, ceftaroline and ceftaroline M-1 CL_R were time-independent.

Summary of safety results

No deaths or serious adverse events (SAEs) were reported in this study. One healthy volunteer (placebo) was prematurely withdrawn from the study due to an AE: mild ventricular extrasystoles, considered to be related to the investigational product by the Investigator. At least 1 AE was reported for 10 healthy volunteers (62.5%) on ceftaroline fosamil in Cohort 1 and 7 healthy volunteers (46.7%) on ceftaroline fosamil in Cohort 2, and for 6 healthy volunteers (60.0%) on placebo (both cohorts). Overall, at least 1 related AE was reported for 21 healthy volunteers (51.2%): 54.8% of healthy volunteers on ceftaroline fosamil and 40% of healthy volunteers on placebo. No severe AEs were reported.

The proportion of healthy volunteers on ceftaroline fosamil with at least 1 AE was higher in Cohort 1 than in Cohort 2 (62.5% versus 46.7%). The most frequently reported AE was

abnormal urine odour. Infusion site reactions were reported on both ceftaroline fosamil and placebo.

Rash and maculo-papular rash were reported for 1 healthy volunteer on ceftaroline fosamil and 4 healthy volunteers on ceftaroline fosamil, respectively. All these events were considered to be related to the investigational product by the Investigator. One event of maculo-papular rash was reported in Cohort 1 (considered to be moderate in severity) and all other events were reported in Cohort 2 (all considered to be mild in severity). The onset time of the events ranged from 3.324 to 9.028 days from the start of treatment (first investigational product administration). All of these events resolved.

No changes in laboratory measurements were considered clinically relevant by the Investigator or reported as AEs. No trends over time and between treatments were observed in mean and median vital signs measurements and no clinically significant abnormal electrocardiogram (ECG) measurements were reported.