Clinical Study Report Synopsis

Drug Substance Ceftaroline fosamil

Study Code D3720C00015

Edition Number 1

EudraCT Number 2001-003999-36

A Phase I, Single-centre, 2-part, Randomised, 2-way Crossover Study to Assess the Local Tolerability and Safety (Multiple-dose) and to Assess the Pharmacokinetics, Safety, and Tolerability (Single-dose) of Ceftaroline in Healthy Subjects when Ceftaroline Fosamil is Diluted in Various Infusion Volumes

Study dates: First subject enrolled: 8 May 2012
Last subject last visit: 6 September 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**
Part A Primary	Safety	To evaluate the local tolerability of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions)	Local infusion site tolerability
Part A Secondary	Safety	To evaluate the safety of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions)	Adverse events; laboratory measurements; vital signs; electrocardiogram; and physical examination.
Part B Primary	Pharmacokinetic	To characterise the pharmacokinetic of ceftaroline in healthy volunteers following a single dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes	C_{max}; t_{max}; AUC; $AUC_{(0-t)}$; $AUC_{(0-12)}$; λ_z; $t_{½\lambda z}$; MRT; apparent CL; apparent V_z; apparent V_{ss}; $R_{M/D,Cmax}$, and $R_{M/D,AUC(0-t)}$ (exposure ratios of ceftaroline/ceftaroline fosamil, adjusted for molecular weight differences); and individual ratios of Treatment A/Treatment C for ceftaroline AUC, $AUC_{(0-t)}$, $AUC_{(0-12)}$, and C_{max}.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Part B Secondary	Pharmacokinetic	To characterise the pharmacokinetic of ceftaroline fosamil (the prodrug of ceftaroline) and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) in healthy volunteers following a single dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes	For both ceftaroline fosamil and ceftaroline M-1: C_{max}; t_{max}; $AUC_{(0-t)}$; and individual ratios of Treatment A/Treatment C for $AUC_{(0-t)}$, and C_{max}. For ceftaroline M-1 only: $AUC_{(0-12)}$; AUC; λ_z; $t_{½\lambda z}$;MRT; $R_{M/D,Cmax}$, $R_{M/D,AUC(0-t)}$, $R_{M/D,AUC(0-12)}$, and $R_{M/D,AUC}$ (exposure ratios of ceftaroline M-1/ceftaroline, adjusted for molecular weight differences); and individual ratios of Treatment A /Treatment C for AUC and $AUC_{(0-12)}$.
Part B Secondary	Safety	To evaluate the safety and tolerability of ceftaroline in healthy volunteers following a single dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes	Adverse events; local infusion site tolerability; laboratory measurements; vital signs; electrocardiogram; and physical examination.

λ_z: apparent terminal elimination rate constant; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-12)}$: area under the plasma concentration-time curve from zero to 12 hours after the start of the infusion; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; CL: total body clearance of drug from plasma; C_{max}: maximum plasma concentration; MRT: mean residence time; $R_{M/D,AUC}$: AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline; $R_{M/D,Cmax}$: C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline; $t_{1/2\lambda z}$: half-life associated with the terminal slope; t_{max}: time to maximum plasma concentration; V_{ss}: volume of distribution at steady state; V_z: volume of distribution based on the terminal phase.
Notes:
Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume (test)
Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)
The molecular weights applied in pharmacokinetic calculations were 684.7 for ceftaroline fosamil, 604.7 for ceftaroline, and 622.7 for ceftaroline M-1.

Study design

Part A

Part A had a placebo-controlled, double-blind, multiple-dose, 2-way crossover design to assess the local tolerability of ceftaroline following multiple infusions of ceftaroline fosamil 600 mg and placebo, each in 50 mL (test) and 250 mL (reference) infusion volumes. The healthy volunteers were randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences of various infusion volumes of ceftaroline fosamil 600 mg and placebo. The investigational product was administered as simultaneous, bilateral, 60-minute infusions every 12 hours over 72 hours, for a total of 6 infusions, followed by a washout of at least 4.5 days (approximately

108 hours) and another simultaneous, bilateral, 60-minute infusion (in different veins than used previously) every 12 hours over 72 hours, for a total of 6 infusions.

The following treatments were administered: Treatment A (600 mg ceftaroline fosamil in 50 mL infusion volume); Treatment B (placebo in 50 mL infusion volume [test]); Treatment C (600 mg ceftaroline fosamil in 250 mL infusion volume [reference]); and Treatment D (placebo in 250 mL infusion volume).

Part B

Part B was conducted following Part A and had an open-label, single dose, 2-way crossover design to evaluate the pharmacokinetics of ceftaroline in either 50 mL and 250 mL infusion volumes or 100 mL and 250 mL infusion volumes, depending on the local tolerability results from Part A. The healthy volunteers were randomly assigned in a 1:1 ratio to either treatment sequence CA or AC. The arm infused in the first period switched for the second and thus the randomisation was stratified by the ordering of infusion to balance any potential arm effects, and to avoid confounding arm with period effects. A single dose of 600 mg ceftaroline fosamil from the appropriate treatment was administered intravenously over 60 minutes on Day 1. Following a 1-day washout (Day 2), a single dose of 600 mg ceftaroline fosamil from the appropriate treatment was administered intravenously over 60 minutes on Day 3.

Treatment A and Treatment C were administered in Part B.

Target subject population and sample size

Part A

Planned: up to 32 healthy volunteers

Randomised: 24 healthy volunteers

Analysed: 24 healthy volunteers

Part B

Planned: up to 10 healthy volunteers

Randomised: 10 healthy volunteers

Analysed: 10 healthy volunteers

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

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Batch number
Ceftaroline fosamil	600 mg of ceftaroline fosamil a pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20 mL vial	FACTA Pharmaceutical S.p.A	206419/01

Duration of treatment

Part A

Six infusions every 12 hours for 3 days in each arm per treatment period

Part B

Single infusion in each arm per treatment period

Statistical methods

The occurrence of infusion site reactions (ISRs) was listed with Visual Infusion Phlebitis (VIP) score by infusion volume/treatment combination across all assessments. The ISR incidence (number and percent of subjects) was presented by infusion volume (50 mL or 250 mL) and treatment (ceftaroline fosamil or placebo) combination. Incidence was also cross-tabulated as occurrence (yes/no) across for active versus placebo by infusion volume and treatment.

Continuous safety variables (clinical chemistry, haematology, and vital signs) were summarised for the safety analysis set using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) by scheduled time point. Categorical variables (AEs and urinalysis) were summarised in frequency tables (frequency and proportion).

Pharmacokinetic analyses were performed in Part B of the study to characterise the pharmacokinetics of ceftaroline, ceftaroline fosamil and ceftaroline M-1. Plasma concentrations of each analyte were summarised by nominal time point using descriptive statistics including the population size (N for sample size and n for available data), geometric mean, geometric coefficient of variation, arithmetic mean, standard deviation, median, minimum, and maximum. Plasma pharmacokinetic parameters and ratios were summarised by analyte and treatment using descriptive statistics including: N, n, geometric mean, geometric coefficient of variation, arithmetic mean, standard deviation, median, minimum, and maximum. No formal statistical hypothesis testing was performed.

Subject population

All healthy volunteers in this study were eligible to be enrolled and randomised.

A total of 24 healthy volunteers were randomised in Part A, of which 4 healthy volunteers were prematurely discontinued from treatment due to ISRs, however, these healthy volunteers were not discontinued from the study and completed all the planned assessments. As stipulated in the Clinical Study Protocol (CSP), if any healthy volunteer had an ISR with a VIP score of 2 or more, the infusion was to be stopped on that arm (treatment discontinued) and the ISR was to be recorded as an adverse event (AE).

A total of 10 healthy volunteers randomised in Part B and all 10 healthy volunteers (100.0%) completed all the investigational product administrations and the study.

Summary of pharmacokinetic results

Ceftaroline

Ceftaroline pharmacokinetic parameters are summarised in Table S3.

Table S3 Summary of plasma ceftaroline pharmacokinetic parameters [geometric mean (%CV)]

Parameters (units)	Treatment A (600 mg ceftaroline fosamil in 50 mL infusion volume) n = 10	Treatment C, reference (600 mg ceftaroline fosamil in 250 mL infusion volume) n = 10
AUC (µg·h/mL)	66.8 (19.5%)	65.4 (22.6%)
$AUC_{(0-t)}$ (µg·h/mL)	66.3 (19.7%)	65.0 (22.7%)
$AUC_{(0-12)}$ (µg·h/mL)	65.3 (18.5%)	64.1 (21.5%)
C_{max} (µg/mL)	29.1 (11.8%)	28.2 (15.5%)
t_{max} (h) [a]	0.97 (0.97 – 0.98)	1.08 (0.97 – 1.08)
λ_z (1/h)	0.288 (18.9%)	0.289 (22.7%)
$t_{1/2\lambda z}$ (h)	2.41 (19%)	2.40 (22.9%)
MRT (h)	2.81 (17%)	2.80 (15.7%)
Apparent CL (L/h)	7.94 (19.5%)	8.10 (22.5%)
Apparent V_z (L)	27.6 (7.8%)	28.1 (9.2%)
Apparent V_{ss} (L)	22.3 (10.4%)	22.7 (11.6%)
$R_{M/D,Cmax}$	10.8 (25.9%)	12.1 (29.1%)
$R_{M/D,AUC(0-t)}$	32.4 (25.8%)	34.9 (31.9%)
Treatment A / Treatment C $AUC_{(0-t)}$ ratio	1.02 (5.7%)	n/a
Treatment A / Treatment C $AUC_{(0-12)}$ ratio	1.02 (5.6%)	n/a
Treatment A / Treatment C AUC ratio	1.02 (5.7%)	n/a
Treatment A / Treatment C C_{max} ratio	1.03 (9.2%)	n/a

n/a not applicable.
[a] t_{max}: median (range) presented

There were no differences in ceftaroline disposition and exposures between the 2 treatments. All pharmacokinetic parameter estimates in Treatment A were comparable to those in Treatment C. In both treatments, after adjusting for molecular weight differences, ceftaroline maximum concentration (C_{max}) and overall exposure ($AUC_{(0-t)}$) were approximately 10-fold and 35-fold those of ceftaroline fosamil.

Individual and geometric mean maximum and overall exposures in Treatment A were similar to Treatment C. Geometric means of Treatment A / Treatment C ratios for C_{max}, $AUC_{(0-t)}$, $AUC_{(0-12)}$, and AUC were between 1.02 to 1.03.

Ceftaroline fosamil

Ceftaroline fosamil pharmacokinetic parameters are summarised in Table S4.

Table S4 Summary of plasma ceftaroline fosamil pharmacokinetic parameters [geometric mean (%CV)]

Parameters (units)	Treatment A (600 mg ceftaroline fosamil in 50 mL infusion volume) n = 10	Treatment C, reference (600 mg ceftaroline fosamil in 250 mL infusion volume) n = 10
$AUC_{(0-t)}$ (µg·h/mL)	2.32 (29.3%)	2.11 (47.5%)
C_{max} (µg/mL)	3.06 (27.4%)	2.64 (39.8%)
t_{max} (h) [a]	0.97 (0.33 - 0.98)	0.97 (0.33 - 1.08)
Treatment A / Treatment C $AUC_{(0-t)}$ ratio	1.10 (42.4%)	n/a
Treatment A / Treatment C C_{max} ratio	1.16 (37.4%)	n/a

n/a not applicable.
[a] t_{max}: median (range) presented

Maximum ceftaroline fosamil concentrations were generally observed at the end of the infusion. However, individual t_{max} values were variable, with maximum concentrations reached earlier during the infusion in some profiles from both treatments (ranging from 0.33 to 0.98 hour in Treatment A and 0.33 to 1.08 hours in Treatment C). Geometric means of Treatment A / Treatment C ratios for C_{max} and $AUC_{(0-t)}$ were 1.16 and 1.10, respectively. The individual Treatment A / Treatment C exposure ratios show high between-subject variability, with differences ranging from a 44.1% decrease to a 96% increase for C_{max} and a 39% decrease to a 144% increase for $AUC_{(0-t)}$.

Ceftaroline M-1

Ceftaroline M-1 pharmacokinetic parameters are summarised in Table S5.

Table S5 Summary of plasma ceftaroline M-1 pharmacokinetic parameters [geometric mean (%CV)]

Parameters (units)	Treatment A (600 mg ceftaroline fosamil in 50 mL infusion volume) n = 10	Treatment C, reference (600 mg ceftaroline fosamil in 250 mL infusion volume) n = 10
AUC (µg·h/mL)	12.1 (19.1%)	11.7 (18.4%)
C_{max} (µg/mL)	1.21 (15.1%)	1.19 (13.3%)
t_{max} (h) [a]	4.00 (3.00 - 4.02)	3.50 (3.00 - 4.00)
$t_{1/2\lambda z}$ (h)	4.17 (15.1%)	4.15 (17.1%)
MRT (h)	7.88 (9.2%)	7.83 (10.1%)
Treatment A / Treatment C AUC ratio	1.03 (5.7%)	n/a
Treatment A / Treatment C C_{max} ratio	1.02 (4.7%)	n/a

n/a not applicable.
[a] t_{max}: median (range) presented

There were no differences in ceftaroline M-1 pharmacokinetic parameters between Treatment A and Treatment C. Maximum and overall exposures of ceftaroline M-1, adjusted for molecular weight differences, represented a small fraction relative to those of ceftaroline (<5% for C_{max} and <20% for $AUC_{(0-t)}$, $AUC_{(0-12)}$, and AUC).

As observed with ceftaroline, individual and geometric mean maximum and overall exposures of ceftaroline M-1 in Treatment A were similar to Treatment C. Geometric means of Treatment A / Treatment C ratios for C_{max}, $AUC_{(0-t)}$, $AUC_{(0-12)}$, and AUC were between 1.02 to 1.04.

Summary of safety results

No deaths or serious adverse events (SAEs) were reported in either Part A or Part B. In Part A, 4 healthy volunteers were prematurely discontinued from treatment in 1 arm, 1 healthy volunteer due to infusion site thrombosis and 3 healthy volunteers due to infusion site phlebitis. These ISRs were all reported on the placebo arm and no ISRs were reported while the healthy volunteers were receiving a 50 mL or 250 mL ceftaroline fosamil infusion.

The frequency of ISRs in Part A is presented in Table S6.

Table S6 Frequency of infusion site reaction occurrence

	Number (%) of subjects			
	Ceftaroline		Placebo	
VIP score	50 mL	250 mL	50 mL	250 mL
0	17 (70.8)	21 (87.5)	19 (79.2)	18 (75.0)
1	7 (29.2)	3 (12.5)	3 (12.5)	4 (16.7)
2	0 (0.0)	0 (0.0)	2 (8.3)	1 (4.2)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

VIP score: 0=No signs of phlebitis; 1=Possibly first signs of phlebitis; 2=Early stage of phlebitis; 3=Medium stage of phlebitis; 4=Advanced stage of phlebitis or the start of thrombophlebitis; 5=Advanced stage of thrombophlebitis.
%: percentage of subjects; VIP: Visual Infusion Phlebitis.

No signs of phlebitis were reported for most of the healthy volunteers, with some cases of possible first signs of phlebitis or early stage phlebitis. The infusion site appeared healthy for most of the healthy volunteers.

At least 1 AE was reported for 9 healthy volunteers (37.5%) in Part A: 4 healthy volunteers (16.7%) on 50 mL ceftaroline fosamil/250 mL placebo and 6 healthy volunteers (25.0%) on 250 mL ceftaroline fosamil/50 mL placebo (1 healthy volunteer reported an AE on both treatments). At least 1 AE was reported for 3 healthy volunteers (30.0%) in Part B: 1 healthy volunteer (10.0%) on 50 mL ceftaroline fosamil and 3 healthy volunteers (30.0%) on 250 mL ceftaroline fosamil (1 healthy volunteer reported an AE on both treatments).

At least 1 AE considered related to the investigational product by the Investigator was reported for 7 healthy volunteers (29.2%) in Part A and for 2 healthy volunteers (20.0%) in Part B. All of the AEs reported on 50 mL ceftaroline fosamil/250 mL placebo in Part A were considered to be related to the investigational product by the Investigator. All AEs were considered to be mild in severity by the Investigator.

Laboratory changes outside the predefined criteria were reported in both Part A and Part B, but none were considered to be clinically relevant by the Investigator. No trends over time and between treatments were observed in mean and median vital signs measurements in both Part A and Part B. No clinically significant abnormal electrocardiogram (ECG) measurements were reported in either Part A or Part B.