AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00012
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An Open-label, Nonrandomised, Phase I Study to Assess the Pharmacokinetics of Ceftaroline After Intravenous Administration of a Single Dose of Ceftaroline Fosamil (200 mg) to Patients with End-stage Renal Disease Undergoing Haemodialysis when Compared to a Single Dose of Ceftaroline Fosamil (600 mg) to a Matched Control Population with Normal Renal Function

Study dates: First subject enrolled: 07 February 2013
Last subject last visit: 30 November 2013

Phase of development: Clinical pharmacology (I)

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

Study centre

One study centre in the United Kingdom

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	PK	To characterise the PK of ceftaroline after intravenous infusion of ceftaroline fosamil in patients with ESRD and a matched control population with normal renal function, and to characterise the clearance of ceftaroline by haemodialysis.	C_{max}, C_{max}/Dose, t_{max}, AUC, AUC/Dose, $AUC_{(0-t)}$, $AUC_{(0-t)}$/Dose, $AUC_{(0-12)}$, $AUC_{(0-12)}$/Dose, $AUC_{(1-5)}$, λ_z, $t_{1/2\lambda z}$, MR_{Cmax}, $MR_{AUC(0-t)}$, MRT, CL/F, V_z/F, V_{ss}/F, E, A_D (interval, cumulative, and overall [$A_{D(1-5)}$]), f_D (interval, cumulative, and overall [$f_{D(1-5)}$]), CL_D (interval and overall)
Secondary	Safety	To evaluate the safety and tolerability of a single intravenous infusion of ceftaroline fosamil in patients with ESRD undergoing intermittent haemodialysis.	Adverse events, safety laboratory assessments, physical examination, 12-lead electrocardiogram, vital signs
	PK	To characterise the PK of ceftaroline fosamil (the prodrug of ceftaroline) and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) after intravenous infusions of ceftaroline fosamil, in patients with ESRD undergoing intermittent haemodialysis and a matched control population with normal renal function.	C_{max}, C_{max}/Dose, t_{max}, AUC, AUC/Dose, $AUC_{(0-t)}$, $AUC_{(0-t)}$/Dose, $AUC_{(0-12)}$, $AUC_{(0-12)}$)/Dose, $AUC_{(1-5)}$, λ_z, $t_{1/2\lambda}z$, MR_{Cmax}, $MR_{AUC(0-t)}$, E, A_D (interval, cumulative, and overall [$A_{D(1-5)}$]), f_D (interval, cumulative, and overall [$f_{D(1-5)}$]), CL_D

λ_z: terminal rate constant; A_D: amount of analyte extracted unchanged into the dialysate; $A_{D(1-5)}$: amount of analyte extracted unchanged into the dialysate overall for the entire haemodialysis session (time: 1.25 to 5.25 hours after the start of infusion); AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-12)}$: area under the plasma concentration-time curve from zero (ie, start of infusion) to 12 hours after the start of the infusion; $AUC_{(1-5)}$: area under the plasma concentration-time curve from 1.25 to 5.25 hours after the start of infusion; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to time of last quantifiable concentration; CL_D: haemodialysis clearance; CL/F: apparent clearance of ceftaroline from plasma; C_{max}: maximum plasma concentration; E: extraction coefficient; ESRD: end-stage renal disease; f_D: percent of dose recovered in dialysate; $f_{D(1-5)}$: percent of dose recovered in dialysate overall for the entire haemodialysis session (time: 1.25 to 5.25 hours after the start of infusion); $MR_{AUC(0-t)}$: $AUC_{(0-t)}$ ratio of ceftaroline/ceftaroline fosamil and ceftaroline M 1/ceftaroline; MR_{Cmax}: C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline; MRT: mean residence time; PK: pharmacokinetics; $t_{1/2\lambda z}$: terminal half-life; t_{max}: time to

maximum concentration; V_{ss}/F: volume of distribution of ceftaroline at steady state; V_z/F: volume of distribution of ceftaroline based on the terminal phase

Dose-normalised exposure parameters, $MR_{AUC(0-t)}$, MR_{Cmax} , and f_D for ceftaroline and ceftaroline M-1 and other dose-dependent PK parameters for ceftaroline were adjusted for molecular weight differences between ceftaroline fosamil (684.7), ceftaroline (604.7), and ceftaroline M-1 (622.7) as appropriate.

CL_D was derived from dialysate recovery data (primary method) and E (Fick's principle, secondary method), as follows:

Primary method: $CL_D = A_{D(1-5)} / AUC_{(1-5)}$

Secondary method: $CL_D = Q*(1-Hct)*E$

where, Q is the flow rate of blood through the dialyser, Hct is the averaged haematocrit values obtained at predose and 8 hours postdose (relative to the start of the infusion), and E is extraction coefficient. For the purpose of this calculation, distribution into red blood cells is assumed to be negligible and blood to plasma conversions are based on haematocrit only.

Study design

This was an open-label, nonrandomised, Phase I, single dose study to assess the PK, safety, and tolerability of ceftaroline fosamil in male and female patients with ESRD requiring intermittent haemodialysis (Group 1). A group of healthy male and female volunteers with normal renal function and similar demographics (Group 2) were recruited to provide within-study reference data.

The following terminology is used to refer to the different subject groups:

- Group 1: patients
- Group 2: healthy volunteers
- Group 1 and Group 2 combined: subjects

Group 1 consisted of patients with ESRD who received a single intravenous infusion of 200 mg ceftaroline fosamil after the end of haemodialysis in Period 1 and prior to haemodialysis in Period 2 (separated by a washout of at least 1 week) in order to study these patients under haemodialysis and nondialysis conditions. Group 2 consisted of healthy volunteers who participated in 1 treatment period.

The study consisted of a screening period (Day -28 to Day -2), residential period (2 treatment periods, Day -1 to Day 3 [Group 1] or 1 treatment period, Day -1 to Day 2 [Group 2]), and a follow-up period (7 to 10 days after discharge from the study centre).

Target subject population and sample size

Male and female subjects aged 18 to 75 years (inclusive) with a body mass index (BMI) between 18 and 35 kg/m^2 and weight between 50 and 110 kg were included in the study. Patients with ESRD in Group 1 had to have a creatinine clearance by Cockcroft-Gault of <15 mL/min or be on haemodialysis, and healthy volunteers in Group 2 had to have a creatinine clearance by Cockcroft-Gault of >80 mL/min.

To ensure that the age (18 to 75 years [inclusive]), weight (50 to 110 kg), and gender distribution of Group 2 were as closely matched to Group 1 as possible, Group 2 was recruited after an appropriate number of patients in Group 1 had completed the study.

One patient in Group 1 was prematurely withdrawn from the study based on her own decision. The patient only received a single infusion in Period 1. As a result, the sponsor and the principal investigator decided not to dose the matching healthy volunteer in Group 2 and the total number of healthy volunteers who received treatment in Group 2 was therefore 7 healthy volunteers, instead of 8 healthy volunteers as planned in the protocol.

Planned: 8 patients with ESRD in Group 1 and 8 healthy volunteers with normal renal function in Group 2.

Analysed: 8 patients with ESRD in Group 1 and 7 healthy volunteers with normal renal function in Group 2.

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

Group 1: single intravenous infusion of 200 mg ceftaroline fosamil, infused over 1 hour (1 infusion in Period 1 at least 1 hour after the end of haemodialysis and 1 infusion in Period 2 before haemodialysis with haemodialysis starting 15 minutes after the end of the infusion).

Group 2: single intravenous infusion of 600 mg ceftaroline fosamil, infused over 1 hour.

Batch number: 207160/01

Duration of treatment

Group 1: 1 infusion in Period 1 after haemodialysis and 1 infusion in Period 2 before haemodialysis (separated by a washout of at least 1 week)

Group 2: single infusion

Statistical methods

Data were generally listed and summarised by renal function group (and further stratified by period for ESRD patients). Continuous variables were summarised using descriptive statistics (N for sample size and n for available data, mean, standard deviation [SD], minimum, median, and maximum). Pharmacokinetic variables (concentrations, and PK parameters, except for t_{max}) also included geometric mean and geometric coefficient of variation (CV%). Means, SD, and CV% were not reported for t_{max}. Pharmacokinetic concentration data also included lower and upper SD bounds which were defined as exp(m±s) where m and s were the mean and SD, respectively, of the natural log-transformed data.

Plasma and dialysate PK concentrations and parameters were summarised by analyte, renal function group, and period, as appropriate, using descriptive statistics. Figures of observed and dose-normalised C_{max}, AUC, and $AUC_{(0-t)}$ were presented by analyte for visual

comparisons of systemic exposures in healthy volunteers and in ESRD patients under nondialysis and dialysis conditions.

All safety data (scheduled and unscheduled) were presented in the data listings and summarised, as appropriate. The adverse events (AEs) were summarised by Preferred Term (PT) and System Organ Class (SOC) by renal function group and across all renal function groups.

Subject population

A total of 15 subjects received treatment: Group 1: 8 patients in Period 1 and 7 patients in Period 2; Group 2: 7 healthy volunteers.

One patient in Group 1, Subject E0001014, prematurely discontinued treatment and was prematurely withdrawn from the study. The patient withdrew based on her own decision. The patient only received a single infusion of 200 mg ceftaroline fosamil on Day 1 of Period 1.

The mean age, weight, and distribution of gender were well matched for the groups. In Group 1 most patients were Black or African American (75.0%) and in Group 2 most healthy volunteers were White (85.7%). The mean BMI was higher for Group 1 (28.95 kg/m^2) compared to Group 2 (25.80 kg/m^2).

Summary of pharmacokinetic results

Ceftaroline

Summary of key plasma and dialysate ceftaroline PK parameters is presented in Table S2.

Table S2 Summary of ceftaroline plasma pharmacokinetic parameters in healthy volunteers and ESRD patients and dialysate recoveries in ESRD patients Period 2 (geometric means [CV%]) (Pharmacokinetic analysis set)

Parameter (unit)	Healthy volunteers (N = 7) GM (CV%)	ESRD patients, nondialysis (Period 1) (N = 8) GM (CV%)	ESRD patients, dialysis (Period 2) (N = 7) GM (CV%)
C_{max}/Dose (µg/mL/mg)	0.0515 (13.5)	0.0635 (14.0)	0.0664 (22.2)
AUC/Dose (µg·h/mL/mg)	0.118 (9.6)	0.366 (38.9)	0.174 (20.9)
C_{max} (µg/mL)	27.3 (13.5)	11.2 (14.0)	11.7 (22.1)
t_{max} (h)	1.00 (1.00 – 1.02)	1.00 (1.00 – 1.08)	1.02 (0.78 – 1.08)
AUC (µg·h/mL)	62.7 (9.4)	64.8 (38.9)	30.7 (20.8)
$t_{1/2\lambda z}$ (h)	2.17 (9.1)	6.13 (23.2)	6.56 (12.9)
CL/F (L/h)	8.45 (9.5)	2.73 (38.8)	5.76 (20.8)
$f_{D(1-5)}$ (%)	ND	ND	73.2 (18.9)
$A_{D(1-5)}$ (mg)	ND	ND	129 (19.1)
CL_D (L/h) (primary method)	ND	ND	11.9 (22.6)

CV%: coefficient of variation; GM: geometric mean; ND: not determined.
$A_{D(1-5)}$: amount of ceftaroline extracted into the dialysate overall for the entire haemodialysis session (time: 1.25 to 5.25 hours after the start of infusion); $f_{D(1-5)}$: percent of dose recovered in dialysate overall for the entire haemodialysis session (time: 1.25 to 5.25 hours after the start of infusion)
Median (range) presented for t_{max}
Group/dialysis condition:
Normal renal function: CrCL >80 mL/min; single dose 600 mg ceftaroline fosamil 1-hour intravenous infusion
End-stage renal disease (ESRD): CrCL <15 mL/min and haemodialysis 3 to 4 times per week
ESRD (Nondialysis) Period 1: single dose 200 mg ceftaroline fosamil 1-hour intravenous infusion; infusion starts at least 1 hour after the end of haemodialysis
ESRD (Dialysis) Period 2: single dose 200 mg ceftaroline fosamil 1-hour intravenous infusion; haemodialysis starts 15 minutes after the end of the infusion

Elimination of ceftaroline was significantly reduced in ESRD patients in Period 1 (nondialysis) compared to healthy volunteers, while there were no major changes in dose-normalised C_{max} and t_{max}. The t_{max} was typically observed at the end of the infusion in all groups and periods.

Ceftaroline $t_{1/2\lambda z}$ in ESRD patients during Period 1 (nondialysis) was approximately 3-fold that of healthy volunteers. The decreased elimination resulted in 3-fold higher dose-normalised AUC such that observed AUC in ESRD patients following a single 1-hour infusion of 200 mg ceftaroline fosamil was similar to AUC in healthy volunteers following a single 1-hour infusion of 600 mg ceftaroline fosamil.

In Period 2 (dialysis), following a 4-hour haemodialysis session that started 15 minutes after the end of infusion of 200 mg ceftaroline fosamil, AUC was approximately half of the AUC in Period 1 (nondialysis) while there were no major changed in C_{max}. The $t_{1/2\lambda z}$ was estimated at time points after haemodialysis ended and was similar to Period 1 (nondialysis).

Haemodialysis efficiently removed ceftaroline. Ceftaroline CL_D calculated from recovery data (primary method) was 11.9 L/h. The CL_D calculated using the secondary method (Fick's principle) was consistent with the primary results and remained stable during the haemodialysis session. A majority of the dose was recovered in dialysate as ceftaroline. Over the 4-hour haemodialysis session that started 15 minutes after the end of the infusion, approximately 73.2% of the dose was recovered in dialysate as ceftaroline.

Ceftaroline fosamil

Summary of key plasma ceftaroline fosamil PK parameters is presented in Table S3.

Table S3 Summary of ceftaroline fosamil plasma pharmacokinetic parameters in healthy volunteers and ESRD patients (geometric means [CV%]) (Pharmacokinetic analysis set)

	Healthy volunteers (N = 7)	ESRD patients, nondialysis (Period 1) (N = 8)	ESRD patients, dialysis (Period 2) (N = 6)
Parameter (unit)	**GM (CV%)**	**GM (CV%)**	**GM (CV%)**
C_{max}/Dose (µg/mL/mg)	0.00540 (23.0)	0.00265 (62.3)	0.00341 (50.4)
$AUC_{(0-t)}$/Dose (µg·h/mL/mg)	0.00419 (22.8)	0.00192 (71.6)	0.00287 (19.2)
C_{max} (µg/mL)	3.24 (23.0)	0.530 (62.3)	0.681 (50.6)
t_{max} (h)	0.67 (0.33 – 1.00)	0.73 (0.33 – 1.00)	0.52 (0.33 – 0.78)
$AUC_{(0-t)}$ (µg·h/mL)	2.51 (22.8)	0.384 (71.6)	0.574 (19.2)

CV%: coefficient of variation; GM: geometric mean
Median (range) presented for t_{max}
Group/dialysis condition:
Normal renal function: CrCL >80 mL/min; single dose 600 mg ceftaroline fosamil 1-hour intravenous infusion
End-stage renal disease (ESRD): CrCL <15 mL/min and haemodialysis 3 to 4 times per week
ESRD (Nondialysis) Period 1: single dose 200 mg ceftaroline fosamil 1-hour intravenous infusion; infusion starts at least 1 hour after the end of haemodialysis
ESRD (Dialysis) Period 2: single dose 200 mg ceftaroline fosamil 1-hour intravenous infusion; haemodialysis starts 15 minutes after the end of the infusion

Ceftaroline fosamil was rapidly eliminated from the systemic circulation in both ESRD patients and healthy volunteers. Quantifiable ceftaroline fosamil concentrations were measured up to 1.5 hours in healthy volunteers, up to 1.25 hours in ESRD patients Period 1 (nondialysis) and up to 1.08 hours in ESRD patients Period 2 (dialysis).

Decreases of approximately 60% or less in ceftaroline fosamil dose-normalised C_{max} and dose-normalised total exposures were observed in ESRD patients during Period 1 (nondialysis) compared to healthy volunteers. Higher exposures, approximately 70% increase for C_{max} and 80% increase for $AUC_{(0-t)}$, were observed when ceftaroline fosamil was administered to ESRD patients in Period 2 (dialysis) compared to Period 1 (nondialysis) at the same 200 mg single dose level.

Ceftaroline M-1

Summary of key plasma and dialysate ceftaroline M-1 PK parameters is presented in Table S4.

Table S4 Summary of ceftaroline M-1 plasma pharmacokinetic parameters in healthy volunteers and ESRD patients and dialysate recoveries in ESRD patients Period 2 (geometric means [CV%]) (Pharmacokinetic analysis set)

	Healthy volunteers (N = 7)	ESRD patients, nondialysis (Period 1) (N = 8)	ESRD patients, dialysis (Period 2) (N = 7)
Parameter (unit)	**GM (CV%)**	**GM (CV%)**	**GM (CV%)**
C_{max}/Dose (µg/mL/mg)	0.00177 (28.6)	0.00828 (31.4)	0.00247 (16.7)
$AUC_{(0-t)}$/Dose (µg·h/mL/mg)	0.0161 (37.9)	0.179 (18.7)	0.0540 (14.2)
C_{max} (µg/mL)	0.965 (28.7)	1.51 (31.4)	0.449 (16.8)
t_{max} (h)	3.25 (3.25 – 5.25)	8.00 (8.00 – 8.03)	12.00 (8.00 – 12.10)
$AUC_{(0-t)}$ (µg·h/mL)	8.79 (37.9)	32.6 (18.8)	9.82 (14.3)
$t_{1/2\lambda z}$ (h)	4.19 (8.7)	8.82 (23.6)	ND
$f_{D(1-5)}$ (%)	ND	ND	7.07 (23.1)
$A_{D(1-5)}$ (mg)	ND	ND	12.9 (23.1)
CL_D (L/h) (primary method)	ND	ND	11.5 (28.8)

CV%: coefficient of variation; GM: geometric mean; ND: not determined.
$A_{D(1-5)}$: amount of ceftaroline M-1 extracted into the dialysate overall for the entire haemodialysis session (time: 1.25 to 5.25 hours after the start of infusion); $f_{D(1-5)}$: percent of dose recovered in dialysate overall for the entire haemodialysis session (time: 1.25 to 5.25 hours after the start of infusion)
Median (range) presented for t_{max}
There was insufficient data to calculate $t_{1/2\lambda z}$ for ESRD patients in Period 2; this parameter was estimable in only 1 of 7 patients.
Group/dialysis condition:
Normal renal function: CrCL >80 mL/min; single dose 600 mg ceftaroline fosamil 1-hour intravenous infusion
End-stage renal disease (ESRD): CrCL <15 mL/min and haemodialysis 3 to 4 times per week

ESRD (Nondialysis) Period 1: single dose 200 mg ceftaroline fosamil 1-hour intravenous infusion; infusion starts at least 1 hour after the end of haemodialysis
ESRD (Dialysis) Period 2: single dose 200 mg ceftaroline fosamil 1-hour intravenous infusion; haemodialysis starts 15 minutes after the end of the infusion

Ceftaroline M-1 formation was increased while elimination was reduced in ESRD patients. When ceftaroline fosamil was administered to ESRD patients in Period 1 (nondialysis), $t_{1/2\lambda z}$ was approximately 2-fold the matched healthy volunteers. Both dose-normalised C_{max} and dose-normalised total exposures ($AUC_{(0-t)}$) were substantially increased, 4.68-fold and 11.1-fold, respectively, those of healthy volunteers. The t_{max} was shifted later by 4.75 hours.

In Period 2 (dialysis), following a 4-hour haemodialysis session that started 15 minutes after the end of infusion of 200 mg ceftaroline fosamil, ceftaroline M-1 maximum and total exposures were decreased to approximately one third of those in Period 1 (nondialysis). The C_{max} was reached at a later time in Period 2 (dialysis) than in Period 1 (nondialysis), t_{max} of 12.00 hours versus 8.00 hours, respectively.

Ceftaroline M-1 CL_D calculated from recovery data (primary method) was 11.5 L/h and similar to that of ceftaroline. The overall $f_{D(1-5)}$ for ceftaroline M-1 was 7.07%, approximately 10% of $f_{D(1-5)}$ for ceftaroline.

In total, approximately 80% of the administered ceftaroline fosamil dose was recovered in dialysate as ceftaroline (73.2%) and ceftaroline M-1 (7.07%) over a 4-hour dialysis period.

Summary of safety results

In Group 1, the number and percentage of patients reporting AEs in Period 1 and Period 2 were similar. In Group 2, the number and percentage of healthy volunteers reporting AEs were similar to the number and percentage of patients reporting AEs in each period for Group 1.

One patient (Subject E0001015) in Group 1 reported an SAE during Period 1 (moderate hyperkalaemia). The SAE was considered to be unrelated to the investigational product by the investigator and resolved the same day. This patient was not withdrawn and completed the study.

Overall, the most frequently reported AE by PT in Group 1 was lethargy (2 patients [25.0%]). Overall, all other AEs by PT for Group 1 were each reported by only 1 patient. Per period, no AE was reported by more than 1 patient.

The most frequently reported AE by PT in Group 2 was rhinitis (2 healthy volunteers [28.6%]). The only other AE reported for Group 2 was upper respiratory tract infection (1 healthy volunteer [14.3%]).

Only 1 AE, frequent bowel movements reported by 1 patient (Subject E0001018) in Group 1 during Period 1, was considered by the investigator to be related to the investigational product.

Only 1 AE, the SAE of hyperkalaemia reported Subject E0001015 in Group 1 during Period 1, was considered by the investigator to be moderate in intensity. All other AEs were mild in intensity.

No relevant changes or trends were noted over time or between groups for safety laboratory variables, vital signs measurements, 12-lead electrocardiogram (ECG) findings, and physical examination findings.