AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00005
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A Phase I, Single Center, Open Label, Two Groups Study to Assess the Safety and Pharmacokinetics of Ceftaroline in Healthy Chinese Volunteers Following Single and Multiple Administration of 600 mg Ceftaroline Fosamil as 60-minute Intravenous Infusion Every 12 hours and as 120-minute Intravenous Infusion Every 8 hours

Study dates:	First subject enrolled: 20 October 2011 Last subject last visit: 09 April 2012
Phase of development:	Clinical pharmacology (I)

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

Study center

This was a single-center study conducted in Beijing, China.

Publications

There were no publications at the time of writing this report.

Objectives and criteria for evaluation

Table S1 presents a summary of the study objectives and variables.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary		
To characterize the PK of ceftaroline in healthy Chinese volunteers following single and multiple administration of 600 mg ceftaroline fosamil	Plasma PK variables Single dose: AUC, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, CL, MRT, $t_{½}$, V_{ss} ,V_z, and Kel Multiple dose: AUC, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, $C_{ss,\,max}$, $C_{ss,\,min}$, $C_{ss,\,av}$, t_{max}, CL, MRT, $t_{½}$, V_{ss}, V_z, $AR_{(Cmax)}$, $AR_{(AUC)}$, Kel, TCP, and DF Urine PK variables: A_e, f_e, and CL_R	PK
Secondary		
To evaluate the safety and tolerability of ceftaroline in healthy Chinese healthy volunteers following single and multiple administration of 600 mg ceftaroline fosamil	Adverse events, vital signs, ECG, laboratory values, physical examination	Safety
To characterize the PK of ceftaroline fosamil and the ceftaroline metabolite (ceftaroline M-1) in healthy Chinese volunteers following single and multiple administration of 600 mg ceftaroline fosamil	Plasma PK variables Single dose: AUC, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, CL, MRT, $t_{½}$, V_{ss} ,V_z, and Kel Multiple dose: AUC, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, $C_{ss,\,max}$, $C_{ss,\,min}$, $C_{ss,\,av}$, t_{max}, CL, MRT, $t_{½}$, V_{ss}, V_z, $AR_{(Cmax)}$, $AR_{(AUC)}$, Kel, TCP, and DF Urine PK variables: A_e, f_e, and CL_R	PK

A_e Cumulative amount excreted in urine; $AR_{(Cmax)}$ Accumulation ratio $C_{ss,max}/C_{max}$; $AR_{(AUC)}$ Accumulation ratio $AUC_{0-\tau,\,multiple\,dose}/AUC_{0-\tau,\,single\,dose}$; AUC Area under the plasma concentration-time curve from time 0 to infinity; $AUC_{(0-\tau)}$ Area under the plasma concentration-time curve during a dosing interval; $AUC_{(0-t)}$ Area under the plasma concentration-time curve from time 0 to time t; CL Total body clearance; CL_R Renal clearance; C_{max} Maximum (peak) plasma concentration; $C_{ss,\,av}$ Average plasma concentration during steady-state dosing interval; $C_{ss,\,max}$ Maximum (peak) plasma concentration at steady state; $C_{ss,\,min}$ Minimum plasma concentration at steady state; DF Degree of fluctuation during steady-state dosing interval; ECG Electrocardiogram; f_e % fraction excreted; Kel Terminal elimination constant; MRT Mean residence time; PK Pharmacokinetic; $t_{½}$ Terminal half-life; TCP Temporal parameter change; t_{max} Time to reach C_{max}; V_{ss} Volume of distribution at steady state; V_z Volume of distribution based on the terminal phase.

Study design

This was a Phase I, single-center, open-label study to assess the pharmacokinetics (PK) and safety of ceftaroline fosamil following single and multiple administration of 600 mg ceftaroline fosamil as 60-min intravenous (iv) infusion every 12 hours (q12h) and as 120-min iv infusion every 8 hours (q8h) in healthy male and female Chinese volunteers. Approximately 24 healthy volunteers were to be enrolled into 2 cohorts (approximately

12 volunteers in each cohort) to obtain at least 10 evaluable volunteers for each cohort. The cohorts were to be enrolled sequentially. The Principal Investigator and AstraZeneca team representatives from medical science and PK reviewed the safety data after the last volunteer from Cohort I (q12h cohort) had completed the drug administration phase, to determine if the next sequential cohort (Cohort II [q8h cohort]) could be enrolled as planned. The safety data was summarized and made available to the Independent Ethics Committee.

Target subject population and sample size

The target population was healthy male or female Chinese volunteers between the age of 18 years and 45 years with a body mass index between and including 19 kg/m^2 and 24 kg/m^2 and weighing at least 50 kg. No formal sample size calculation was done for this study. A sample size of 10 evaluable volunteers for each cohort was considered sufficient to characterize the PK of ceftaroline fosamil and provide safety and tolerability data in Chinese healthy volunteers.

Investigational product: dosage, mode of administration and batch numbers

Ceftaroline fosamil 600 mg (the prodrug of ceftaroline) was administered as an iv infusion over 60 min or 120 min depending on the cohort. The batch number for ceftaroline fosamil was 0012D1.

Duration of treatment

In the q12h cohort, the volunteers received a single 600 mg ceftaroline fosamil 60-min iv infusion in the morning on Day 1 and Day 8. On Day 3 to Day 7, they received 600 mg ceftaroline fosamil as a 60-min iv infusion q12h. On Day 2, volunteers did not receive the drug, but plasma and urine PK samples were obtained. In the q8h cohort, the volunteers received a single 600 mg ceftaroline fosamil 120-min iv infusion in the morning on Day 1 and Day 8. On Day 2 to Day 7, they received 600 mg ceftaroline fosamil as a 120-min iv infusion q8h.

Statistical methods

To achieve the primary and secondary objectives in PK, the PK of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 was evaluated by assessment of drug concentrations in plasma and urine. These drug concentrations were listed and summarized for each dosing period using the geometric mean (Gmean), coefficient of variation (CV), arithmetic mean, standard deviation (SD), minimum, maximum, number of observations, and number of observations <LLOQ (lower limit of quantification). The PK parameters except for T_{max} were summarized for each cohort using Gmean, CV, arithmetic mean, SD, minimum, maximum, and number of observations. T_{max} was summarized for each cohort using median, minimum, maximum, and number of observations. The plasma and urine PK parameters analyzed are listed in Table S1.

To achieve the secondary objective in safety and tolerability, adverse events (AEs), vital signs, physical examinations, ECGs, and clinical laboratory assessments were evaluated. All safety data were summarized in a descriptive analysis. Baseline was the last assessment before dose. All AEs were summarized for each cohort by preferred term and system organ

class of the Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 for the dosing period. All serious adverse events (SAEs) and discontinuations from investigational treatment were summarized using the MedDRA version 15.0, as well as provided individual narratives and/or line listings.

Subject population

A total of 51 healthy volunteers were enrolled into the study at 1 site in China. Of these, 26 volunteers received treatment with ceftaroline fosamil. The volunteers were recruited in 2 cohorts: 12 volunteers in the q12h cohort and 14 volunteers in the q8h cohort; 2 volunteers were added to the q8h cohort in order to ensure 10 evaluable volunteers. A total of 24 (92.3%) volunteers completed the study. One volunteer from each cohort was discontinued from the study due to AE of rash.

The demographic and key baseline characteristics were comparable between the 2 cohorts. The mean age of the volunteers in the study was 30.9 years (range 19 years to 41 years). The average weight was 60.85 kg (range 51 kg to 74 kg) with an average body mass index of 21.97 kg/m^2 (range 19.1 kg/m^2 to 23.9 kg/m^2). Concomitant medications used by the volunteers due to treatment-emergent AEs were not considered to have impacted the PK or safety conclusions of this study.

Summary of pharmacokinetic results

PK parameters for ceftaroline by cohort and study day are summarized in Table S2. Both ceftaroline C_{max} and AUC were similar, both on Day 1 and Day 8 for both dosing regimens. Accumulation of ceftaroline with regard to C_{max} and AUC was minor for both, the q12h and q8h dosing regimens, despite the 50% increase in daily dose (1200 mg/day versus 1800 mg/day). Approximately 70% of the given dose was recovered as ceftaroline in urine after both q12h and q8h dosing regimens. Renal clearance (CL_R) of ceftaroline was also similar after a single iv administration (q12h: 5.93 L/h; q8h: 5.69 L/h), and at the dosing interval at steady state (q12h: 5.86 L/h; q8h: 5.85 L/h), with low variability (CV<20%).

Ceftaroline fosamil was rapidly eliminated from plasma. Rapid conversion of prodrug was complete shortly post infusion after both dosing regimens. There were no quantifiable plasma concentrations in the 30-min sample post infusion after single or repeated iv administrations with either the q12h or the q8h dosing regimens. No prodrug was quantified in urine after 600 mg iv infusions of either 60 min q12h or 120 min q8h.

Ceftaroline M-1 showed accumulation in plasma after both the q12h and the q8h dosing regimens, which was more pronounced after the more frequent q8h dosing. Both C_{max} and AUC increased at steady state after both dosing regimens. The accumulation ratios for C_{max} and AUC were 1.3 (30%) after the q12h iv infusions, and 1.6 to 1.8 (60% to 80%) after the q8h iv infusions, indicating some accumulation. The CL, V_z, V_{ss}, and $t_{½}$ of ceftaroline M-1 were similar between single doses and after repeated dosing, indicating time-independent PK. The urinary excretion of ceftaroline M-1 also indicated accumulation between a single dose and at steady state. The CL_R was similar after a single dose (q12h: 4.02 L/h; q8h: 3.92 L/h)

and at steady state (q12h: 4.35 L/h; q8h: 4.21 L/h), with relatively low variability (CV<25%), indicating time-independent PK.

Table S2 Pharmacokinetic parameters for ceftaroline by dose cohort and study day (Single-dose PK analysis set)

Cohort I/Day 1	Statistic	AUC (ug*h/mL)	C_{max} (ug/mL)	$AR_{(AUC)}$	V_z (L)	V_{ss} (L)	CL (L/h)	$t_{1/2}$ (h)
	n	11	11	NA	11	11	11	11
	Gmean*	65.43	27.58	NA	26.4	19.1	8.1	2.26
	CV (%)	17.06	13.37	NA	12.3	13.4	14.8	11.8
	Amean	66.22	27.79	NA	26.6	19.2	8.2	2.27
	SD	11.29	3.72	NA	3.3	2.6	1.2	0.27
	Median	63.12	26.30	NA	27.0	19.3	8.4	2.25
Cohort I/Day 8	Statistic	$AUC_{(0-12)}$ (ug*h/mL)	$C_{ss,max}$ (ug/mL)	$AR_{(AUC)}$	V_z (L)	V_{ss} (L)	CL (L/h)	$t_{1/2}$ (h)
	n	11	11	11	11	11	11	11
	Gmean*	66.17	27.52	1.0	26.6	19.0	8.0	2.30
	CV (%)	15.67	12.62	7.4	13.5	13.9	14.6	10.6
	Amean	66.88	27.72	1.0	26.8	19.1	8.1	2.31
	SD	10.48	3.50	0.1	3.6	2.7	1.2	0.25
	Median	64.93	28.90	1.0	28.0	18.3	8.2	2.33
Cohort II/Day 1	Statistic	AUC (ug*h/mL)	C_{max} (ug/mL)	$AR_{(AUC)}$	V_z (L)	V_{ss} (L)	CL (L/h)	$t_{1/2}$ (h)
	n	14	14	NA	14	14	14	14
	Gmean*	66.50	20.97	NA	25.1	18.8	8.0	2.18
	CV (%)	11.17	10.87	NA	13.2	11.6	10.0	7.1
	Amean	66.86	21.08	NA	25.3	19.0	8.0	2.19
	SD	7.46	2.29	NA	3.3	2.2	0.8	0.16
	Median	66.70	20.90	NA	25.0	18.8	7.9	2.23
Cohort II/Day 8	Statistic	$AUC_{(0-8)}$ (ug*h/mL)	$C_{ss,max}$ (ug/mL)	$AR_{(AUC)}$	V_z (L)	V_{ss} (L)	CL (L/h)	$t_{1/2}$ (h)
	n	13	13	13	13	13	13	13
	Gmean*	67.20	22.22	1.1	25.2	18.6	7.9	2.21
	CV (%)	7.91	7.82	7.2	11.5	9.6	7.6	7.4
	Amean	67.39	22.28	1.1	25.3	18.7	7.9	2.22
	SD	5.33	1.74	0.1	2.9	1.8	0.6	0.16
	Median	66.95	22.40	1.1	24.6	18.4	7.9	2.25

Cohort I: 600 mg ceftaroline fosamil as 60-minute iv infusion. Single dose on Days 1 and 8, and q12h dose on Days 3 to 7.
Cohort II: 600 mg ceftaroline fosamil as 120-minute iv infusion. Single dose on Days 1 and 8, and q8h dose on Days 2 to 7.
* Geometric mean was calculated using transformed data.
Amean Arithmetic mean; $AR_{(AUC)}$ Accumulation ratio $AUC_{0-\tau, \text{multiple dose}}/AUC_{0-\tau, \text{single dose}}$; AUC Area under the plasma concentration-time curve from time 0 to infinity; $AUC_{(0-8)}$ Area under the plasma concentration-time curve from time 0 to 8 hours; $AUC_{(0-12)}$ Area under the plasma concentration-time curve from time 0 to 12 hours; $AUC_{0-\tau}$ Area under the plasma concentration-time curve during a dosing interval;

C_{max} Maximum (peak) plasma concentration; $C_{ss,max}$ Maximum (peak) plasma concentration at steady state; CL Total body clearance; CV Coefficient of variation; Gmean geometric mean; iv Intravenous; NA Not applicable; PK Pharmacokinetic; q8h Every 12 hours; q12h Every 12 hours; SD Standard deviation; $t_{1/2}$ Terminal half-life; V_{ss} Volume of distribution at steady state; V_z Volume of distribution based on the terminal phase. Source: Table 11.2.2.1 to Table 11.2.2.4.

Summary of safety results

Overall, 22 volunteers (11 from each cohort) experienced at least 1 AE during the study of which 18 volunteers (9 volunteers from each cohort) experienced at least 1 AE causally related to ceftaroline as assessed by the investigator. No volunteer had an AE leading to death in this study. Four volunteers in the q12h cohort experienced SAEs, whereas there were none in the q8h cohort. Two volunteers (1 volunteer in each cohort) were discontinued from the study treatment due to the AE of rash. The majority of the reported AEs were mild (n=11 [42.3%]) or moderate (n=10 [38.5%]) in intensity, and only 1 volunteer in the q12h cohort experienced an AE of rash of severe intensity.

Rash was the most frequently reported AE (5/12 volunteers in the q12h cohort and 6/14 volunteers in the q8h cohort), and is a known reaction to ceftaroline. It was observed at a similar frequency between the 2 cohorts. The pattern of rash was typical for the cephalosporin class of drugs, and occurred more frequently in young healthy volunteers. In most of the cases, the onset of rash was later in the study towards end of treatment or after the end of study treatment. Mild increases in transaminases were observed during treatment, mainly in the q8h cohort. The increases seen were in line with the known effects of ceftaroline, and increases in transaminases are expected for the cephalosporin class. In all the cases, the transaminase levels returned back to normal levels after end of treatment.

The AE profile associated with administration of ceftaroline in healthy Chinese volunteers was similar to the known safety profile of ceftaroline and the cephalosporin class. No new or major safety or tolerability concerns related to administration of ceftaroline fosamil in healthy Chinese volunteers were identified from AE reporting, laboratory parameters, vital signs, electrocardiogram variables, or physical examination findings.