AstraZeneca

PROTOCOL SYNOPSIS

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 centre(s) and number of subjects planned

This study will be conducted at 1 study centre in the United Kingdom. A minimum of 8 healthy volunteers and 8 patients with end-stage renal disease will be enrolled at the study centre.

Study period		**Phase of development**
Estimated date of first subject enrolled	Q3 2012	Clinical Pharmacology (1)
Estimated date of last subject completed	Q1 **2014**	

Objectives

Primary objective

To characterise the pharmacokinetics of ceftaroline after intravenous infusion of ceftaroline fosamil in patients with end-stage renal disease and a matched control population with normal renal function and to characterise the clearance of ceftaroline by haemodialysis.

Secondary objectives

1. To evaluate the safety and tolerability of a single intravenous infusion of ceftaroline fosamil in patients with end-stage renal disease undergoing intermittent haemodialysis

2. To characterise the pharmacokinetics 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 end-stage renal disease undergoing intermittent haemodialysis and a matched control population with normal renal function

Study design

This is an open-label, nonrandomised, Phase I, single dose, study to assess the pharmacokinetics, safety, and tolerability of ceftaroline in 8 patients with end-stage renal disease requiring intermittent haemodialysis (Group 1). A group of 8 healthy volunteers with normal renal function and similar demographics (Group 2) will be recruited to provide within-study reference data.

The study will consist 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).

Group 1 will receive a single intravenous dose of 200 mg ceftaroline fosamil infused over 1 hour on Day 1 of Period 1. In Period 1 the infusion will take place at least 1 hour after the end of haemodialysis and 48 hours before the next scheduled haemodialysis. In Period 2, a single intravenous dose of 200 mg ceftaroline fosamil will be infused over 1 hour on Day 1, prior to the haemodialysis session. Haemodialysis will then start 15 minutes after the end of the infusion, within a ±5 minutes time window. Patients will be resident in the study centre from Day -1 to Day 3 of each treatment period. Period 1 and Period 2 will be separated by a washout of at least 1 week.

Group 2 will receive a single intravenous dose of 600 mg ceftaroline fosamil infused over 1 hour on Day 1. Healthy volunteers will be resident in the study centre from Day -1 to Day 2 of the treatment period.

Target subject population

Male subjects and female subjects aged 18 to 75 years (inclusive) will be enrolled in the study. Patients with end-stage renal disease who require haemodialysis 3 to 4 times per week with a creatinine clearance by Cockcroft-Gault of <15 mL/min will be enrolled in Group 1. Male and female healthy volunteers will be enrolled in Group 2. To ensure that the age, weight, and gender distribution of Group 2 are as closely matched to Group 1 as possible (age to be within ±5 years and weight to be within ±20% of Group 1), Group 2 will be recruited after **an appropriate number of subjects in** Group 1 have completed the study.

Investigational product, dosage and mode of administration

Group 1: 200 mg ceftaroline fosamil infused intravenously over 1 hour.

Group 2: 600 mg ceftaroline fosamil infused intravenously over 1 hour.

Duration of treatment

Group 1: 1 single intravenous dose of 200 mg ceftaroline fosamil infused over 1 hour (1 infusion in each treatment period). Period 1 and Period 2 will be separated by a washout of at least 1 week.

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

Outcome variable(s):

- Pharmacokinetics

  All Subjects

  The following plasma pharmacokinetic parameters of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 will be determined for all subjects and periods, unless otherwise indicated: maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), area under the plasma concentration-time curve from zero to infinity (AUC), area under the plasma concentration-time curve from zero to time of the last quantifiable concentration ($AUC_{(0-t)}$), area under the plasma concentration-time curve from zero to 12 hours after the start of the infusion ($AUC_{(0-12)}$), terminal rate constant (λ_z), terminal half-life ($t_{1/2\lambda z}$), dose-normalised C_{max}, dose-normalised AUC, dose-normalised $AUC_{(0-t)}$, and dose-normalised $AUC_{(0-12)}$, C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline (MR_{Cmax}), AUC ratios of ceftaroline M-1/ceftaroline (MR_{AUC}).

  In addition, the following plasma pharmacokinetic parameters will be calculated for ceftaroline and ceftaroline fosamil: mean residence time (MRT), total body clearance of drug from plasma (CL for ceftaroline fosamil, apparent CL for ceftaroline), volume of distribution based on the terminal phase (V_z for ceftaroline fosamil, apparent V_z for ceftaroline), volume of distribution at steady-state (V_{ss} for ceftaroline fosamil, apparent V_{ss} for ceftaroline).

  End-stage Renal Disease Patients During Haemodialysis (Period 2) only

  The following additional ceftaroline and ceftaroline M-1 pharmacokinetic parameters will be calculated, unless otherwise noted: area under the plasma concentration-time curve from 75 minutes to 5.25 hours after the start of the infusion ($AUC_{(1-5)}$), amount of drug extracted unchanged into the dialysate (A_D) during each 1-hour interval, cumulatively, and overall ($A_{D(1-5)}$) for the entire haemodialysis session (time: 75 minutes to 5.25 hours after the start of infusion); percent of dose recovered in dialysate (f_D,%) during each 1-hour interval,

cumulatively, and overall ($f_{D(1-5)}$,%) for the entire haemodialysis session (time: 75 minutes to 5.25 hours after the start of infusion), extraction coefficient (E) at each time point during haemodialysis (for ceftaroline fosamil, ceftaroline, and ceftaroline M-1), haemodialysis clearance (CL_D) calculated from recovery data (primary method) and based on Fick principle (secondary method). In addition, E will be calculated for the endogenous markers blood urea nitrogen and creatinine.

- Safety

  Adverse events, safety laboratory variables, physical examination, 12-lead electrocardiogram, and vital signs

Statistical methods

Pharmacokinetic data and parameters will be listed, summarised using descriptive statistics, and presented graphically by analyte, renal function group, and period, as appropriate.

Tabulations and listings of data for adverse events, vital signs, physical examinations, clinical laboratory tests, and electrocardiograms will be presented. For clinical laboratory tests, listings of values for each subject will be presented with abnormal or out-of-range values flagged (other than those associated with renal impairment and/or stable chronic condition).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study clinical study protocol.

Abbreviation or special term	Explanation
$\%AUC_{ex}$	Percent of AUC which is extrapolated to infinity
λ_z	Terminal rate constant
A_D	Amount of drug extracted unchanged into the dialysate
$A_{D(1-5)}$	Amount of drug extracted unchanged into the dialysate overall for the entire haemodialysis session (time: 75 minutes to 5.25 hours after the start of infusion)
AE	Adverse event (see definition in Section 6.3.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
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 75 minutes to 5.25 hours after the start of infusion
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to time of the last quantifiable concentration
BCRP	Breast cancer resistance protein
BLQ	Below the lower limit of quantification
BMI	Body mass index
BUN	Blood urea nitrogen
C_a	Predialyser plasma concentration
CABP	Community-acquired bacterial pneumonia
CAP	community-acquired pneumonia
CHMP	Committee for Medicinal Products for Human Use
CL	Total body clearance of drug from plasma
CL_D	Haemodialysis clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CrCL	Creatinine clearance

Abbreviation or special term	Explanation
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
cSSSI	Complicated skin and skin structure infections
cSSTI	Complicated skin and soft tissue infections
C_v	Postdialyser plasma concentration
CV%	Coefficient of variation
CYP	Cytochrome P450
DAE	Discontinuation of the investigational product due to an AE
DBP	Diastolic blood pressure
E	Extraction coefficient
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
ESRD	End-stage renal disease
$f_{D,}$%	Percent of dose recovered in dialysate
$f_{D(1-5),}$%	Percent of dose recovered in dialysate ($f_{D,}$%) overall for the entire haemodialysis session (time: 75 minutes to 5.25 hours after the start of infusion)
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hct	Haematocrit
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
LH	Luteinising hormone
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR_{AUC}	AUC ratios of ceftaroline M-1/ceftaroline

Abbreviation or special term	Explanation
MR_{Cmax}	C_{max} ratio of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline
MRT	Mean residence time
NA	Not applicable
ND	Not determined
NDA	New Drug Application
OAE	Other significant AE (see definition in Section 11.1.1)
OAT	Organic anion transporter
OCT	Organic cation transporter
PBP	Penicillin-binding protein
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
Q	Flow rate of blood
Rsq	Coefficient of determination for calculation of λ_z
SAE	Serious adverse event (see definition in Section 6.3.2).
SBP	Systolic blood pressure
SD	Standard deviation
$t_{1/2\lambda z}$	Terminal half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum concentration
ULN	Upper limit of normal
USA	United States of America
V_{ss}	Volume of distribution at steady-state
V_z	Volume of distribution based on the terminal phase

1. INTRODUCTION

In August 2009, AstraZeneca entered into a collaboration agreement with Cerexa (a wholly-owned subsidiary of Forest Laboratories) to co-develop and commercialise ceftaroline fosamil in all markets outside the United States of America (USA), Canada, and Japan. Cerexa submitted a New Drug Application (NDA) to the USA Food and Drug Administration (FDA) in December 2009 for the treatment of complicated skin and skin structure infections (cSSSI) and community-acquired bacterial pneumonia (CABP) in adults. This NDA was approved in October 2010 and ceftaroline fosamil is marketed in the US under the brand name Teflaro™. AstraZeneca has submitted a Marketing Authorisation Application of ceftaroline fosamil in the European Union for complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP).

1.1 Background

Preclinical data

Ceftaroline, like other β-lactams, inhibits bacterial cell wall biosynthesis. This occurs through binding of the β-lactam to the transpeptidase active site of penicillin-binding proteins (PBPs), which carry out the final steps in cell wall biosynthesis.

The safety pharmacology program assessed the central nervous system (CNS), cardiovascular, renal, and respiratory effects of ceftaroline fosamil and ceftaroline in vitro and by single dose in vivo studies in rats and monkeys. Consistent with the cephalosporin class, convulsions were the main safety finding in the safety pharmacology program. In vitro human ether-a-go-go-related gene (hERG) and dog Purkinje fiber studies with ceftaroline fosamil and ceftaroline did not result in any findings at clinically relevant concentrations, nor did a telemetry study in monkeys assessing cardiovascular function reveal any drug-related functional changes. However, in clinical studies to date, no convulsions or pro-convulsive behaviour has been observed in patients.

Nonclinical absorption, distribution, metabolism, and excretion studies did not raise any significant issues that adversely impacted on the development of ceftaroline fosamil. Ceftaroline fosamil and/or metabolites were rapidly distributed throughout the body following single doses of radiolabelled ceftaroline fosamil to rats. Ceftaroline was minimally distributed in the erythrocytes. No binding to the melanin-containing skin or tissues of the uveal tract of the eye was observed. After repeated administration of [^{14}C] ceftaroline fosamil for 14 days in rats, the highest concentration of radioactivity was detected in the kidney followed by the skin, and radioactivity concentrations in other tissues were lower than those observed in plasma.

Following a single intravenous dose of [^{14}C] ceftaroline fosamil to rats and monkeys, the dose was excreted in urine predominantly as ceftaroline and its open-ring metabolite, ceftaroline M-1. Only a very small amount (<1%) of ceftaroline fosamil was excreted in the urine of monkeys and ceftaroline fosamil was not observed in rat urine. The transformation of ceftaroline fosamil to ceftaroline and the transformation of ceftaroline to ceftaroline M-1 were

observed in all species studied. Additional minor metabolites observed in the metabolite profiles of human plasma and excreta were also detected in the rat and monkey, ie, no human-specific metabolites were observed.

Clinical data

In its clinical development program, ceftaroline has been evaluated in healthy adult, elderly, and adolescent volunteers, and in patients with mild to severe renal impairment, as well as in patients with end-stage renal disease (ESRD) requiring haemodialysis. The safety and efficacy of ceftaroline treatment has been demonstrated in patients with cSSSI and in patients with moderate to severe CABP.

The clinical development program for ceftaroline fosamil comprised 17 clinical studies, including 2 Phase III cSSSI and 2 Phase III CABP safety and efficacy studies. Approximately 1700 subjects have received ceftaroline fosamil as part of this program. At the recommended administration regimen of 600 mg ceftaroline fosamil administered as a 1-hour intravenous infusion every 12 hours for 5 to 14 days for treatment of cSSSI and 5 to 7 days for treatment of CABP, ceftaroline fosamil was well tolerated and demonstrated a favourable safety profile compatible with treatment of cSSSI and CABP and known cephalosporin class effects. In patients with renal impairment it is appropriate to reduce the dose to 400 mg every 12 hours for patients with moderate renal impairment (creatinine clearance [CrCL]: 30 to 50 mL/min). Insufficient information is available to make specific dose adjustment recommendations in patients with severe renal impairment and ESRD.

The incidences of treatment-emergent adverse events (TEAEs) reported by subjects administered ceftaroline fosamil were similar compared with those reported by subjects administered comparator therapies. The majority of the TEAEs experienced were mild or moderate in severity and were assessed as unrelated to ceftaroline fosamil administration. Furthermore, the incidences of death, serious adverse events (SAEs), and premature discontinuation of ceftaroline fosamil, or withdrawal from the study were low and similar compared with subjects administered comparator therapies.

The safety data revealed that potential adverse cardiac, renal, or hepatic effects with the administration of ceftaroline fosamil were similar to those observed for other cephalosporins. The risk of allergic reactions to ceftaroline appeared to be similar to that of the comparators studied, and although 2 seizures were observed in subjects who received ceftaroline fosamil, both occurred more than 2 days after completion of ceftaroline fosamil treatment. Cephalosporins are known to be associated with positive direct Coombs' test results. Although rates of seroconversion from a negative to a positive direct Coombs' test were higher in the ceftaroline group compared with the comparator groups, no subject was identified with clinical findings or laboratory results that were consistent with haemolytic anaemia. The incidence of potential antibiotic-associated diarrhoea (which can occur with most antibiotics) was low and similar in subjects who received ceftaroline fosamil compared with comparator treatments and resulted in similar numbers of subjects prematurely discontinued from the investigational product or from the study due to TEAEs of diarrhoea in

both treatment groups. Confirmed cases of *Clostridium difficile*-associated diarrhoea were rare in both treatment groups.

At the clinical ceftaroline fosamil doses studied (600 mg intravenous every 12 hours or 400 mg intravenously every 12 hours), ceftaroline demonstrated an acceptable safety profile that was compatible with treatment of cSSSI and CABP. In addition, no safety concerns were identified in the safety review beyond those already known to be cephalosporin class effects.

To date, the maximum single doses of ceftaroline fosamil administered in Phase I studies were 1500 and 2000 mg each in 8 subjects (P903-20) and 1500 mg in 54 subjects (P903-05, QTc study). Multiple total doses of 1800 mg/day have been assessed in 3 healthy volunteer studies: 600 mg every 8 hours administered as 1-hour infusions were assessed over 10 days in 8 subjects (P903-020); 600 mg every 8 hours administered as 1-hour infusions were assessed over 10 days in 8 subjects (Study CXL-PK-01); 900 mg every 12 hours administered as 1-hour infusions were assessed over 10 days in 9 subjects (Study CXL-PK-01). In study CXL-PK-01, ceftaroline fosamil was studied in combination with equal doses of the β-lactamase inhibitor NXL104. These high single and multiple dose studies have not indicated any safety concerns regarding the administration of ceftaroline fosamil.

The cumulative clinical experience with ceftaroline identified the following adverse reactions for ceftaroline as presented in Table 1.

Table 1 Reported adverse events that may be related to ceftaroline (by System Organ Class)[a]

System Organ Class	Adverse event
Blood and lymphatic disorders	Thrombocytopenia, anaemia
Nervous system disorders	Headache, dizziness
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria
Vascular disorders	Phlebitis
Immune system disorders	Hypersensitivity or anaphylaxis
Infections and infestations	*Clostridium difficile* colitis
Investigations	Increased blood creatinine and transaminases, prolonged prothrombin time, International Normalised Ratio increased, Coombs' direct test positive
General disorders and administrative site conditions	Infusion site reactions, erythema, pain, phlebitis, pyrexia

[a] This information appears in Table 10.2-1 of the Investigator's Brochure.

The following is a summary of the basic pharmacokinetic (PK) properties of ceftaroline (following intravenous infusion of ceftaroline fosamil), based on in vitro and in vivo data:

- Rapid conversion of the prodrug, ceftaroline fosamil, by phosphatases to active ceftaroline in plasma
- Low human plasma protein binding (~20%) of ceftaroline with no distribution into erythrocytes
- Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increase approximately proportionally to dose (50 to 1000 mg); with a terminal half-life ($t_{1/2\lambda z}$) of 2 to 3 hours
- Metabolised by opening of ceftaroline fosamil's β-lactam ring to ceftaroline, the microbiologically inactive metabolite M-1 and additional minor unidentified metabolites
- No inhibition or induction of cytochrome P450 (CYP) isoenzymes in vitro
- No metabolism by CYP isoenzymes in vitro
- No accumulation or time-dependent PK observed after repeated infusions every 12 hours
- Eliminated mainly through renal excretion (clearance is approximately equivalent to the glomerular filtration rate)
- Ceftaroline is not a substrate or inhibitor of human active renal uptake transporters, organic cation transporter (OCT)-2, organic anion transporter (OAT)-1, or OAT3, indicating that active secretion of ceftaroline in the kidneys does not contribute significantly to its renal elimination
- Ceftaroline is not a substrate of the efflux of transporters P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), or an inhibitor of P-gp but is a weak inhibitor of BCRP
- No effect on QTc interval
- Little effect on faecal intestinal flora
- No dose-adjustment needed based on gender, age, or mild renal impairment

One study, Study P903-18, has previously been performed in patients with ESRD (n=6); with a control group of healthy volunteers with normal renal function matched for age, gender, and weight. Subjects with ESRD on intermittent haemodialysis received a single dose of 400 mg ceftaroline fosamil infused intravenously over 1 hour on 2 occasions, once before, and once

after haemodialysis with a washout period of ≥7 days in-between. Infusion of the first dose was completed 4 hours before haemodialysis (predialysis). The infusion of the second dose was started at least 60 minutes after the end of haemodialysis (postdialysis). Subjects with normal renal function received a single dose of 400 mg ceftaroline fosamil infused intravenously over 1 hour. Plasma levels of ceftaroline fosamil were substantially higher in subjects with ESRD than subjects with normal renal function, which may be due to the same arm being used for PK sampling and intravenous infusion. The systemic exposure (AUC) was significantly greater in subjects with ESRD than in subjects with normal renal function for both ceftaroline (89% predialysis; 167% postdialysis) and ceftaroline M-1 (231% predialysis; 573% postdialysis). In subjects with ESRD dosed with ceftaroline fosamil before haemodialysis, the $t_{1/2\lambda z}$ was significantly longer for both ceftaroline (123%) and ceftaroline M-1 (2-fold) in subjects with ESRD dosed before or after haemodialysis than in subjects with normal renal function, but the time to maximum concentration (t_{max}) was similar among the treatments. Results of the study showed that haemodialysis could remove ceftaroline and ceftaroline M-1 from plasma.

For further information, please refer to the Investigator's Brochure.

1.2 Rationale for conducting this study

Ceftaroline is cleared predominantly by renal excretion and its PK is altered in patients with moderate or severe renal impairment. Therefore, it is desirable to evaluate the PK of ceftaroline in patients with ESRD and the effects of intermittent haemodialysis. In addition, evaluation of the PK of ceftaroline in this population will allow for an assessment of the amount of ceftaroline that is removed by haemodialysis.

A previously conducted study in patients with ESRD (P903-18) showed that ceftaroline was removed to some extent by haemodialysis but unexplained high concentrations of ceftaroline fosamil were observed during the infusion period in some patients. This present study will further characterise the PK, safety, and tolerability of ceftaroline administered as ceftaroline fosamil after single intravenous infusion to patients with ESRD (Group 1) both while they are undergoing haemodialysis and between haemodialysis sessions. Furthermore, it will aid understanding of the previous observations regarding ceftaroline fosamil levels.

1.3 Benefit/risk and ethical assessment

This study will not provide any direct medical benefits to subjects who participate. The major risk for subjects who participate in the study is from adverse events (AEs) induced by ceftaroline or injection site pain, thrombophlebitis, and infection from numerous PK blood sampling and intravenous needle placement.

In the Phase III clinical studies, the overall incidence of adverse drug reactions is low, and comparable among ceftaroline and the comparators. No AE reactions occurred in >5% of subjects receiving ceftaroline fosamil. The most common adverse reactions occurring in ≥4% of the subjects receiving ceftaroline fosamil in the pooled Phase III clinical studies were diarrhoea, nausea, and headache.

Monitoring will be performed according to Good Clinical Practice (GCP)/International Conference on Harmonisation (ICH) guidelines. Safety data will be collected during the study. In addition, there will be complete data gathering (eg, through questionnaires) to allow proper safety evaluation on the following events, which are currently classified as important potential risks for ceftaroline in the global and European Union Patient Risk Management Plan, if they would occur in the study: haemolytic anaemia, drug-induced liver disease, renal impairment, and seizures.

Clinical laboratory, electrocardiogram (ECG), and vital signs results for subjects in this study will be monitored and clinically significant abnormalities will be reviewed and assessed by the investigator.

The sponsor will immediately notify the principal investigator of important safety data (eg, toxicology, absorption, distribution, excretion, teratology) that becomes available during the study.

2. STUDY OBJECTIVES

2.1 Primary objective

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.

2.2 Secondary objectives

1. To evaluate the safety and tolerability of a single intravenous infusion of ceftaroline fosamil in patients with ESRD undergoing intermittent haemodialysis

2. 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

3. STUDY PLAN AND PROCEDURES

This clinical study protocol (CSP) has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is an open-label, nonrandomised, Phase I, single dose study to assess the PK, safety, and tolerability of ceftaroline 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) will be recruited to provide within-study reference data.

The study will be conducted at 1 study centre in the United Kingdom. A minimum of 8 healthy volunteers and 8 patients with ESRD will be enrolled.

Group 1 will consist of up to 8 patients with ESRD who will participate in 2 treatment periods (separated by a washout of at least 1 week) in order to study these patients under haemodialysis and nondialysis conditions. Group 2 will consist of up to 8 healthy volunteers who will participate in 1 treatment period. Approximately 16 subjects will be screened and enrolled in order to have at least 6 subjects in each group completing the study.

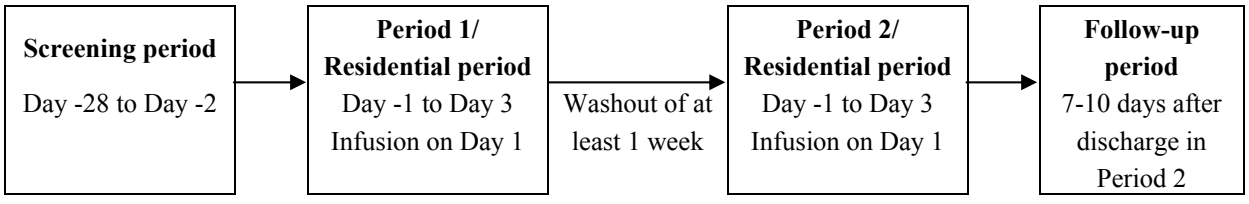
The study will consist of a screening period (Day -28 to Day -2), residential period (2 treatment periods, Day -1 to Day 3 [Group 1] or 1 treatment period, Day -1 to Day 2 [Group 2]), and a follow-up period (7 to 10 days after discharge from the study centre).

Group 1 (patients with ESRD)

After screening, eligible patients will be admitted to the study centre for Period 1 on Day -1 and will receive a single intravenous dose of 200 mg ceftaroline fosamil infused over 1 hour on Day 1. The infusion will start at least 1 hour after the end of a haemodialysis session and 48 hours before the next scheduled haemodialysis. Blood samples will be collected for up to 48 hours after the start of the infusion for the determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1. The patients will remain in the study centre until the completion of the study procedures on Day 3.

After a washout of at least 1 week, patients will be admitted to the study centre on Day -1 for Period 2 and will receive a single intravenous dose of 200 mg ceftaroline fosamil infused over 1 hour on Day 1, prior to the haemodialysis session. Haemodialysis will then start 15 minutes after the end of the infusion, within a ±5 minutes time window. Samples of blood and dialysate will be collected for up to 48 hours after the start of the infusion for the determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1. Blood samples will also be collected at specified time points for haematocrit and endogenous markers including blood urea nitrogen and creatinine. Patients will remain in the study centre until the completion of the study procedures on Day 3. The study design for Group 1 is presented in Figure 1.

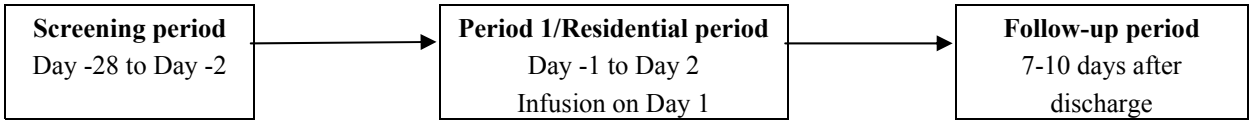
Figure 1 Study design for Group 1



Group 2 (healthy volunteers)

After screening, eligible healthy volunteers will be admitted to the study centre on Day -1 and will receive a single intravenous dose of 600 mg ceftaroline fosamil infused over 1 hour on Day 1. Blood will be collected for up to 24 hours after the start of infusion for the determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1. The healthy volunteers will remain at the study centre until the completion of the study procedures on Day 2. The study design for Group 2 is presented in Figure 2.

Figure 2 Study design for Group 2



Throughout the treatment periods, subjects will be monitored for safety and blood samples for the PK evaluation will be collected.

The schedule of assessments and the PK sampling time points are provided in Table 2 and Figure 3, respectively.

Table 2 Schedule of assessments

Assessment	Screening	Residential period/ treatment period[n]				Follow-up
	Day -28 to -2	Day -1	Day 1	Day 2	Day 3	7-10 days after discharge
Informed consent[a]	X					
Inclusion/exclusion criteria	X	X				
Demographics	X					
Medical, surgical, and smoking history	X					
Luteinising hormone/follicle-stimulating hormone[b]	X					
Estimated creatinine clearance[c]	X	X		X[i]	X[i]	
Hepatitis B, hepatitis C, and HIV	X					
Alcohol and urine drug screen	X	X				
Clinical chemistry and haematology[b]	X	X			X	X
Urinalysis/urine microscopy[d]	X	X				X
Pregnancy test[e]	X	X				X
Physical examination		X			X	
Brief physical examination						X
Height, weight, and BMI calculation[f]	X	X				X
12-Lead electrocardiogram[g]	X	X				X
Admission to study centre		X				
Intravenous infusion of investigational product[h]			X			
Discharge from the study centre[i]				X	X	
Haemodialysis/dialysate collection[j]			X			
Vital signs[k]	X	X	X	X	X	X
Blood collection for pharmacokinetics[l]			X	X	X	
Haematocrit blood sampling for Group 1/Period 2 only[l]			X			
Blood urea nitrogen/creatinine blood sampling during dialysis for Group 1/Period 2 only[l]			X			
Prior and concomitant medication recording	X	X	X	X	X	X

Assessment	Screening	Residential period/ treatment period[n]				Follow-up
	Day -28 to -2	Day -1	Day 1	Day 2	Day 3	7-10 days after discharge
Adverse event/serious adverse event recording[m]	X	X	X	X	X	X

[a] Informed consent will be collected before any study-specific procedures are performed.
[b] The healthy volunteers in Group 2 will fast for 4 hours before the clinical laboratory evaluations at screening and during the residential period. Fasting is not required for the follow-up visit. Luteinising hormone and follicle-stimulating hormone will be measured to determine menopausal status at the screening visit.
[c] Creatinine clearance will be estimated using the Cockroft-Gault formula at the screening visit, admission to the study centre, and at discharge from the study centre.
[d] A urine sample for urinalysis and microscopy will be collected, if possible, along with the other clinical laboratory evaluations.
[e] A serum pregnancy test will be performed for all females. If positive, the subject will be excluded from participation in the study.
[f] Height and weight will be evaluated at the screening visit and BMI will be calculated. Only weight will be evaluated at all other visits.
[g] A 12-lead electrocardiogram will be performed after the subject has rested in the supine position for 10 minutes.
[h] Patients in Group 1 will each receive 2 single intravenous infusions of 200 mg ceftaroline fosamil, infused over 1 hour (1 infusion in each treatment period). Healthy volunteers in Group 2 will each receive 1 single intravenous infusion of 600 mg ceftaroline fosamil, infused over 1 hour.
[i] Subjects will be discharged from the study centre after the completion of all study-related procedures. This will be Day 3 for Group 1 and Day 2 for Group 2.
[j] Only applicable for Group 1, Period 2. The patients will start their scheduled haemodialysis 15 minutes after the end of the 1-hour infusion (within a ±5 minutes time window). Dialysate will be collected over 1-hour intervals throughout the entire haemodialysis session as shown in Figure 4.
[k] Supine blood pressure and pulse rate will be evaluated after the subject has rested in the supine position for at least 10 minutes. If possible, the same arm and the same make and model of equipment should be used for each evaluation. During the residential period, predose blood pressure and pulse rate will be evaluated within 60 minutes before the start of the infusion.
[l] Blood samples will be collected at the time points provided in Figure 3 and Figure 4.
[m] Serious adverse events will be collected from the time of informed consent up to the follow-up visit. Adverse events will be collected from Day 1 until the follow-up visit.
[n] Group 1 will have 2 residential periods/treatment periods (Period 1 and Period 2) and Group 2 will have 1 residential period/treatment period (Period 1).

BMI: body mass index; HIV: human immunodeficiency virus.

Figure 3 Time schedule for pharmacokinetic assessments in Group 1/Period 1 and in Group 2

Study day	Administration of the investigational product	Protocol time (after the start of the infusion)	Scheduled Assessments		
			Group 1/Period 1		Group 2
			Haemodialysis[a]	Blood sample	Blood sample
1			Start ↓ End		
		Predose[b]		X	X
	Start of infusion[a]	0			
	↓	20 minutes		X	X
	↓	40 minutes		X	X
	End of infusion	60 minutes		X[c]	X[c]
		65 minutes		X	X
		75 minutes		X	X
		90 minutes		X	X
		2.25 hours		X	X
		3.25 hours		X	X
		4.25 hours		X	X
		5.25 hours		X	X
		8 hours		X	X
		12 hours		X	X
2		24 hours		X	X
		36 hours		X	
3		48 hours		X	

[a] The infusion will start at least 1 hour after the end of the haemodialysis session and 48 hours before the next scheduled session.

[b] The predose samples will be collected within 1 hour before the start of the infusion.

[c] End of infusion samples will be collected within 2 minutes of the end of the infusion.

Figure 4 Time schedule for pharmacokinetic assessments in Group 1/Period 2

Study day	Administration of the investigational product	Protocol time (after the start of the infusion)	Group 1/Period 2				
			Haemo-dialysis	PK blood sample	Haemato-crit blood sample	BUN/ creatinine blood sample	Dialysate collection[d]
1		Predose[a]		X	X		
	Start of infusion	0					
	↓	20 minutes		X			
	↓	40 minutes		X			
	End of infusion	60 minutes		X[b]			
		65 minutes		X			
		75 minutes	Start	X[c]			X[f]
		90 minutes	↓	X[d,e]		X[d,e]	↓
		2.25 hours	↓	X[d,e]		X[d,e]	X[f]
			↓				↓
		3.25 hours	↓	X[d,e]		X[d,e]	X[f]
			↓				↓
		4.25 hours	↓	X[d,e]		X[d,e]	X[f]
			↓				↓
		5.25 hours	End	X[d,e]		X[d,e]	X[f]
		8 hours		X	X		
		12 hours		X			
2		24 hours		X			
		36 hours		X			
3		48 hours		X			

[a] The predose samples will be collected within 1 hour before the start of the infusion.
[b] End of infusion samples will be collected within 2 minutes of the end of the infusion.
[c] Haemodialysis to start 15 minutes after the end of the infusion, within a ±5 minutes time window; the 75 minute PK sample will be collected just prior to the start of the haemodialysis.
[d] All blood samples collected during and surrounding the haemodialysis session will be collected from both predialyser and postdialyser lines. At each timepoint, the pre- and postdialyser samples should be collected as close as possible in the following sequence: predialyser PK, predialyser BUN/creatinine, postdialyser PK, and post dialyser BUN/creatine samples. The postdialyser sample should be collected within 1 minute of the respective predialyser sample.
[e] The blood samples during haemodialysis session, including protocol times 90 minutes, 2.25 hour, 3.25 hour, and 4.25 hour, should be collected at 15 minutes, 1 hour, 2 hours, and 3 hours after the start of

haemodialysis, respectively; the 5.25 hour (4 hours after start of haemodialysis) samples must be collected just at the end of the haemodialysis session.

[f] Dialysate will be collected in appropriate containers over 1 hour intervals throughout the entire (approximately 4 hours) haemodialysis session (including, 0 to 1, 1 to 2, 2 to 3, 3 to 4 hours after the start of haemodialysis). The blood flow, dialysate flow rate, dialysate volume, type of dialysis membrane, and the make and model of the dialyser will be recorded. The entire dialysate will be collected, its volume recorded, and the primary and backup samples retained for analysis of ceftaroline and ceftaroline M-1 concentrations.

BUN: blood urea nitrogen; PK: pharmacokinetic.

3.2 Rationale for study design, doses and control groups

An open-label, nonrandomised, single dose study design is used to assess the PK, safety, and tolerability of ceftaroline in patients with ESRD requiring intermittent haemodialysis. A group of healthy volunteers with normal renal function and similar demographics will be recruited to provide within-study reference data.

Both male and female patients and healthy volunteers will be screened for the study. The inclusion and exclusion criteria are defined so that the healthy volunteers selected for participation in the study are known to be free from any significant illness.

Ceftaroline fosamil is being developed for the treatment of serious bacterial infections including those caused by aerobic gram-negative and gram-positive pathogens. The extensive clinical programme has established 600 mg infused over 1 hour every 12 hours as an appropriate dose in healthy volunteers with normal renal function. Phase I studies in subjects with various degrees of renal impairment have indicated that it is appropriate to reduce the dose to 400 mg every 12 hours for patients with moderate renal impairment (CrCL: 50 to 80 mL/min). Data from a previous study in patients with ESRD undergoing intermittent haemodialysis (P903-18) has been used to propose that 200 mg every 12 hours as an appropriate dose in this group of patients. Therefore it is considered appropriate to test this dose in the current study. To obtain adequate PK data in the control group with normal renal function, it will be necessary to administer the normal dose of 600 mg.

In a previous study in patients with ESRD (Study P903-18) a single dose of 400 mg of ceftaroline fosamil resulted in a C_{max} and AUC for ceftaroline that were up to 77% and 2.6-fold higher than in the control group of healthy volunteers administered the same dose. However, in comparison with healthy volunteers administered the standard 600 mg dose the C_{max} and AUC values in ESRD patients were up to 4% and 80% higher. Since the dose in this study is 200 mg, the C_{max} and AUC values in the ESRD patients are not expected to exceed those observed in healthy volunteers administered 600 mg ceftaroline fosamil.

In Study P903-18, blood samples for plasma concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 were collected up to 72 hours after start of investigational product administration (ESRD patients had PK draws up to 48 hours during predialysis period and up to 72 hours during after-dialysis period and normal subjects had PK draws up to 48 hours after start of infusion). In ESRD patients dosed before dialysis, 5 of 6 patients had no measurable ceftaroline concentrations at 48 hours postdose. In ESRD patients dosed after dialysis, 4 of

6 patients had measurable ceftaroline concentrations in the 48-hour sample; concentrations dropped to below the lower limit of quantification (BLQ) in all 6 patients at the 60-hour and 72-hour time points. There were no detectable concentrations in the 24-, 36-, and 48-hour samples of the healthy control volunteers. For ceftaroline M-1, in ESRD patients dosed before dialysis, all 6 patients had no measurable concentrations at 48 hours postdose. In ESRD patients dosed after dialysis, 3 of 6 patients had measurable concentrations in the 60-hour sample; ceftaroline M-1 concentrations dropped to BLQ for all 6 patients at the 72-hour time point. In healthy controls, 1 of 6 volunteers had a measurable M-1 concentration in the 24-hour sample and there were no detectable concentrations at the 36- and 48-hour time points. Considering the times of last measurable ceftaroline and ceftaroline M-1 concentrations, the washout period of at least 1 week for ESRD patients in the current study is adequate. In addition, the difference in PK sampling durations for ESRD patients (up to 48 hours) and healthy volunteers (up to 24 hours) is not expected to have a confounding effect on differences in $t_{1/2\lambda z}$, if observed.

As the PK of the ceftaroline-related moieties has been shown to be linear, a single dose of ceftaroline fosamil is considered adequate to define the PK behaviour of ceftaroline fosamil, ceftaroline, and ceftaroline M-1. Mathematical projections from single dose to steady-state conditions will be used to develop administration guidelines for this group of patients.

To obtain adequate PK data in the control group with normal renal function, it will be necessary to give the normal dose of 600 mg. To remove the potential influence of study-specific factors influencing the results, a matched control group of healthy volunteers with normal renal function will be included in the study (Group 2), as recommended in the FDA and Committee for Medicinal Products for Human Use (CHMP) guidelines (FDA Guidance for Industry 2010 and CHMP Note for Guidance 2004). To ensure that the age, weight, and gender distribution of Group 2 are as closely matched to Group 1 as possible (age to be within ±5 years and weight to be within ±20% of Group 1), Group 2 will be recruited after **an appropriate number of subjects in** Group 1 have completed the study.

Considering the primary objective is a PK objective, in which outcomes are not subjected to bias in assessments and data interpretations, the open-label design is deemed appropriate. In addition, due to the nature of the study and the dose selection for ESRD patients undergoing intermittent haemodialysis versus healthy volunteers, randomisation is not applicable to the current study.

4. SUBJECT SELECTION CRITERIA

The principal investigator should keep a record, the subject screening log, of subjects who entered prestudy screening.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, all subjects should fulfil the following criteria:

1. Provision of signed and dated, written informed consent prior to any study-specific procedures

2. Male and female (who are not pregnant or lactating) subjects aged 18 to 75 years (inclusive) with suitable veins for cannulation or repeated venipuncture

3. Females must have a negative pregnancy test at screening and Day -1 (admission to the study centre) and must not be lactating

   - Females of childbearing potential: Females of childbearing potential must have a negative serum pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control (Section 5.1.1) for 3 months before enrolment and until 3 months after the last investigational product administration

   - Females of nonchildbearing potential: Females of nonchildbearing potential are defined as females who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but excluding bilateral tubal occlusion) or who are postmenopausal. Females will be considered postmenopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply: Females under 50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or following cessation of exogenous hormonal treatment and luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels in the postmenopausal range. Females over 50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment

4. Male subjects should be willing to use barrier contraceptives (ie, condoms with spermicide) from the first day of investigational product administration until 3 months after the last investigational product administration

5. Have a body mass index (BMI) between 18 and 35 kg/m^2 and weight between 50 and **110** kg

For inclusion in the study healthy volunteers with normal renal function must fulfil the additional following criterion:

6. Healthy volunteers should have CrCL by Cockcroft-Gault >80 mL/min

For inclusion in the study patients with ESRD must fulfil all the additional following criteria:

7. Stable physical condition, consistent with ESRD, based on the results of the medical history, vital signs, 12-lead ECG, and clinical laboratory evaluations performed within 3 weeks of the first investigational product administration. As a result of renal impairment or underlying disease, certain laboratory parameters may be outside the normal reference ranges

8. CrCL by Cockcroft-Gault of <15 mL/min **or on haemodialysis**

9. Patients who require haemodialysis 3 to 4 times per week and are receiving the same dialysis regimen for at least 1 month before screening

10. Haematocrit level higher than 30% at screening and baseline for each treatment period

11. Concomitant medications to treat underlying diseases or medical conditions related to renal insufficiency are allowed, except when specifically excluded by name or pharmacological class

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study

2. History or presence of gastrointestinal, hepatic, or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs

3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first investigational product administration

4. Any clinically significant abnormalities in clinical chemistry, haematology, or urinalysis results, as judged by the investigator

5. Any positive result at screening for serum hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV)

6. Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG that may interfere with the interpretation of QTc interval changes.

7. Prolonged QTcF **≥500** ms, or shortened QTcF <340 ms, or family history of long QT syndrome

8. Known or suspected history of drug abuse, as judged by the investigator

9. Current smokers, or those who have smoked or within the previous **3** months**. Nicotine replacement products, eg, nicotine patch, nicotine chewing gum are allowed**

10. History of alcohol abuse or excessive intake of alcohol, as judged by the investigator

11. Positive screen for drugs of abuse (patients with ESRD using medications that may cause a positive drug screen will not be excluded, as judged by the investigator), or alcohol at screening or on Day -1 (admission to the study centre) prior to the first investigational product administration

12. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to ceftaroline fosamil, eg, cephalosporins

13. Excessive intake of caffeine-containing drinks eg, coffee, tea, caffeine-containing energy drinks and cola (more than 5 cups of coffee or equivalent per day)

14. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first investigational product administration

15. Plasma donation within 1 month of screening or any blood donation/blood loss >500 mL during the 3 months prior to screening

16. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 3 months of the first investigational product administration in this study. The period of exclusion begins at the time of the last visit of the prior study. Note: subjects who consented and were screened, but did not receive investigational product in this study or a previous phase I study, are not excluded

17. Previous enrolment in the present study

18. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study centre)

19. Judgement by the investigator that the subjects should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of the study data or are considered unlikely to comply with the study procedures, restrictions, and requirements

For healthy volunteers with normal renal function the following are considered additional criteria for exclusion from the study:

20. **Any clinically significant abnormalities in vital signs as judged by the investigator**

21. Use of prescribed or nonprescribed medication including antacids, analgesics other than paracetamol/acetaminophen, herbal remedies, vitamins, and minerals during the 2 weeks prior to the first investigational product administration or longer if the medication has a long half-life. Occasional use of paracetamol/acetaminophen for minor pains and headache, and hormone replacement therapy for females are allowed

For patients with ESRD the following are considered additional criteria for exclusion from the study:

22. Vital signs, after 10 minutes supine rest:

- SBP: 90 to 200 mmHg
- DBP: **50** to 100 mmHg
- Pulse rate: <40 or **≥110** bpm

23. Significant change or addition to routine medication (prescribed or over-the-counter) within 1 month of the first investigational product administration. Minor changes to medications that require frequent dose adjustment, such as insulin or analgesia, can be made up to 2 weeks prior to the first investigational product administration as agreed between the investigator and AstraZeneca

24. Receiving any dialysis treatment other than intermittent haemodialysis

25. Renal transplantation or renal carcinoma within 1 year before screening

26. Requiring immunosuppressive medications, including steroids

27. History of nephrectomy

The procedures for withdrawal of incorrectly enrolled subjects are provided in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions apply for the specified times during the study:

1. The healthy volunteers in Group 2 should fast from at least 4 hours before the clinical laboratory evaluations at screening and during the residential period. Fasting is not required for the follow-up visit

2. Eat and drink only the standardised meals and drinks provided (apart from water) during the residential period in the study centre (a renal diet will be served to patients with ESRD)

3. Abstain from consuming any of the following:

   – Alcohol from 72 hours before Day -1 (admission to the study centre), during the residential period, and for 72 hours before the follow-up visit

   – Energy drinks containing taurine or glucuronolactone eg, Red Bull from 72 hours before Day -1 (admission to the study centre), during the residential period, and for 72 hours before the follow-up visit

   – Caffeine-containing drinks during the residential period, apart from any provided as part of a standardised meal. Excessive intake of caffeine should be avoided between discharge from the study centre and the follow-up visit

   – Poppy seeds found in speciality bread from the time of providing informed consent until after the final medical examination at the follow-up visit

4. Abstain from smoking, and drugs of abuse from the time of providing consent until after the final medical examination at the follow-up visit

5. Subjects should refrain from strenuous physical activity, which is not within the subject's normal daily routine, from 7 days prior to Day -1 (admission to the study centre) until after the final medical examination at the follow-up visit

6. Abstain from blood or plasma donation until 3 months after the final medical examination at the follow-up visit

7. Male subjects should use a condom with spermicide to prevent pregnancy and drug exposure of a partner and refrain from donating sperm or fathering a child from the first investigational product administration until 3 months after the last investigational product administration

Use of concomitant medications is described in Section 5.6.

5.1.1 Highly effective contraceptive methods

Females of childbearing potential must use a highly effective contraceptive method with additional use of a condom by her male partner. The following contraceptive methods are considered to be highly effective:

- Total sexual abstinence

- Vasectomised sexual partner (with participant assurance that the partner received postvasectomy confirmation of azoospermia)

- Tubal occlusion
- Intra-uterine device (provided coils are copper banded)
- Intra-uterine system containing levonorgestrel (eg, Mirena®)
- Medroxyprogesterone injections (eg, Depo-Provera®)
- Etonogestrel slow-release subcutaneous implants (eg, Implanon®, Norplan®)
- Normal or low dose combined oral contraceptives with fixed doses of oestrogen and progestin. Note: Triphasic pills, which have different strength pills in the same pack, are not considered highly effective and are therefore excluded from this instruction
- Norelgestromin/ethinyl estradiol transdermal system (eg, Evra®)
- Intravaginal device containing ethinyloestradiol and etonogestrel (eg, NuvaRing®)
- Cerazette®

Females of childbearing potential must have been stable on a highly effective contraceptive method for at least 3 months prior to screening and continue on this chosen method with additional use of a condom by her male partner until 3 months after the last investigational product administration.

Vomiting within 3 hours of taking oral contraception does pose a risk equivalent to a missed pill. Subjects will be instructed to contact the investigator on how to following the World Health Organization guidelines for a missed pill whenever they suspect unprotected intercourse.

Subjects should be made aware of the availability of emergency "post-coital" contraception if there is an indication for it (eg, missing intra-uterine device threads or a late injection). Acceptable emergency methods of contraception to be used should only include those approved by a regulatory agency in the subject's region.

The birth control method will be verified in the medical records prior to the start of the study (contraceptive history) and females of childbearing potential will be asked to verify compliance at each visit up to 3 months after the last investigational product administration.

5.2 Subject enrolment and initiation of investigational product

The principal investigator will:

1. Obtain signed informed consent from each potential subject before any study-specific procedures are performed

2. Assign a potential subject a unique enrolment number, beginning with 'E#', as an identifier

3. Determine subject eligibility (see Sections 4.1 and 4.2)

If a subject withdraws his/her participation in the study, then his/her enrolment code cannot be reused.

5.3 Procedures for handling subjects incorrectly enrolled or initiated on investigational product

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive investigational product. There can be no exceptions to this rule.

Where a subject who does not meet the inclusion/exclusion criteria is enrolled in error, or incorrectly started on treatment, or where a subject subsequently fails to meet the study criteria after initiation, the investigator should inform the AstraZeneca Clinical Pharmacology Alliance physician immediately. Although the treatment should be discontinued, the subject should be advised to continue assessments to ensure their safety.

5.4 Blinding and procedures for unblinding the study (Not applicable)

5.5 Treatments

5.5.1 Identity of investigational product(s)

The investigational product to be administered in this study is presented in Table 3.

Table 3 Identity of the investigational product

Investigational product	Dosage form and strength	Manufacturer
Ceftaroline fosamil	30 mg/mL intravenous infusion (600 mg)	FACTA Pharmaceutical S.p.A

The investigational product will be supplied by AstraZeneca as 600 mg of ceftaroline fosamil, a sterile pale yellowish-white to light yellow crystalline powder in a single dose clear glass 20 mL vial.

An excipient, L-arginine (approximately 660 mg L-arginine/g of prodrug) will be added as an alkalising agent to maintain the pH of the constituted solution to pH 4.8 to 6.2. The study centre will be responsible for diluting the concentrate to obtain the desired dose level.

For intravenous infusion, ceftaroline fosamil powder (concentrate for solution for infusion) is constituted with sterile water and transferred to an intravenous bag or bottle containing sterile sodium chloride 0.9% for infusion or dilution. The infusion solution is clear ranging in colour from light to dark yellow. Vials of ceftaroline fosamil dry mixture for injection should be stored at 2°C to 8°C until ready for use. Vials should be used before the labelled expiry date.

The diluted intravenous solutions should be administered promptly, however the investigational product has been shown to be physically and chemically stable for 6 hours at 23°C to 25°C, or for 24 hours at 2°C to 8°C, followed by 6 hours at 23°C to 25°C. Therefore, once the constituted vial is diluted in the infusion bag or bottle, it should be administered within 6 hours of the initial constitution, or refrigerated for 24 hours at 2°C to 8°C, then administered within 6 hours when stored below 25°C. Reconstituted solutions and subsequent infusions should be prepared according to a strict aseptic technique.

The staff involved in the dispensing procedure should also be aware that ceftaroline fosamil is a cephalosporin-type drug which carries some safety concerns and should not be handled by staff members with known allergies to this type of product.

Further instructions will be provided to the study centre's pharmacist regarding dose preparation and administration.

5.5.2 Doses and treatment regimens

Patients in Group 1 will each receive 1 single intravenous infusion of 200 mg ceftaroline fosamil, infused over 1 hour (1 infusion in Period 1 and 1 infusion in Period 2).

Healthy volunteers in Group 2 will each receive 1 single intravenous infusion of 600 mg ceftaroline fosamil, infused over 1 hour.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

5.5.4 Storage

All investigational products should be kept in a secure place under appropriate storage conditions. The investigational product label specifies the appropriate storage conditions.

5.6 Concomitant and post-study treatment(s)

Healthy volunteers

Apart from paracetamol/acetaminophen and hormone replacement therapy, no concomitant medication or therapy will be allowed. The healthy volunteers should be instructed that no other concomitant medication is allowed, including antacids, herbal remedies, vitamins, minerals, and over-the-counter products, from 2 weeks before the first investigational product administration (or longer if the medication has a long half-life) until after the final examination at the follow-up visit without the consent of the investigator.

Other medication, which is considered necessary for the healthy volunteer's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the case report form (CRF).

Patients with ESRD

Concomitant medications to treat underlying diseases or medical conditions related to renal insufficiency are allowed, except when specifically excluded by name or pharmacological class.

A significant change or addition to a patient's routine medication (prescribed or over-the-counter) within 1 month of the first investigational product administration will not be allowed. Minor changes to medications that require frequent dose adjustment, such as insulin or analgesia, can be made up to 2 weeks prior to the first investigational product administration as agreed between the investigator and AstraZenenca. However, this should not obviate necessary medical treatment. Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and the AstraZeneca Clinical Pharmacology Alliance physician should be informed. Medications will be recorded in the appropriate sections of the CRF.

5.7 Treatment compliance

The administration of all investigational products should be recorded in the appropriate sections of the CRF.

Treatment compliance will be assured by supervised administration of the investigational product by the investigator or delegate. The dose, date, time of administration of the investigational product, and the duration of the infusion will be recorded and checked by the monitor at the monitoring visits.

5.7.1 Accountability

The investigational products provided for this study will be used only as directed in the CSP.

The study centre's staff will account for all investigational products received at the study centre, administered to the subjects, and returned to the pharmacy.

Study centre's staff, if applicable or the AstraZeneca monitor will account for all investigational products received at the study centre, unused investigational products and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.8 Discontinuation of investigational product and withdrawal from the study

Subjects may be discontinued from investigational product in the following situations

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Severe noncompliance to CSP

5.8.1 Procedures for discontinuation of a subject from investigational product

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by the investigator. Adverse events will be followed up (see Sections 6.3.3 and 6.3.4).

Patients in Group 1 who withdraw from the study will be replaced at the discretion of AstraZeneca if fewer than 6 patients have completed both treatment periods.

Healthy volunteers in Group 2 who withdraw from the study will be replaced at the discretion of AstraZeneca if fewer than 6 healthy volunteers have completed the treatment period

If a subject withdraws his/her participation in the study, then his/her enrolment code cannot be reused.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timings of these assessments are detailed in Table 2 and Figure 3.

It is important that PK sampling occurs at the precise CSP-scheduled time. In order to achieve this, other assessments scheduled at the same time may be started prior to the time point. The preferred sequence at a particular time point is:

- 12-Lead ECG
- Blood pressure and pulse rate
- Blood sample collection for PK. In addition, for Group 1 Period 2, at each time point during the haemodialysis, the pre- and postdialyser samples should be collected as close as possible in the following sequence: predialyser PK, predialyser blood urea nitrogen (BUN)/creatinine, postdialyser PK, and post dialyser BUN/creatine samples. The postdialyser sample should be collected within 1 minute of the respective predialyser sample.
- Safety and laboratory assessments

6.1 Recording of data

The investigator will ensure that data are recorded on the CRFs as specified in CSP and in accordance with the instructions provided.

The investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

The investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study centre.

6.2 Data collection at enrolment and follow-up

6.2.1 Screening procedures

Each potential subject will provide informed consent at screening prior to starting any study-specific procedures.

The eligibility of subjects will be determined during the screening period. The following assessments will be performed at screening:

- Review of the inclusion/exclusion criteria with each subject
- Recording of demographic data (date of birth, gender, and race)
- Recording of medical/surgical and smoking history
- Recording of concomitant medication
- Recording of SAEs
- A complete physical examination
- Height, weight, and calculation of BMI
- Vital signs (supine blood pressure and pulse rate)
- 12-Lead ECG
- Alcohol screen
- Blood sample for routine clinical chemistry, haematology, and screening for hepatitis B, hepatitis C, and HIV
- Urine sample for routine urinalysis and screening of drugs of abuse
- Estimation of CrCL
- Pregnancy test and determination of menopausal status (LH and FSH) for females only

6.2.2 Follow-up procedures

The assessments performed at the follow-up visit will include recording of concomitant medications, recording of AEs and SAEs, a brief physical examination, vital signs (supine

blood pressure and pulse rate), routine clinical chemistry, haematology, and urinalysis, weight, 12-lead ECG, and a pregnancy test (females only).

6.3 Safety

The principal investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver), or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no investigational product has been administered.

The term AE is used to include both serious and non-serious AEs.

6.3.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix B to the CSP.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from Day 1 throughout the treatment period and including the follow-up visit.

Serious AEs will be recorded from the time of informed consent throughout the treatment period and including the follow-up visit.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
  - Mild (awareness of sign or symptom, but easily tolerated)
  - Moderate (discomfort sufficient to cause interference with normal activities)
  - Severe (incapacitating, with inability to perform normal activities)
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to the investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

The investigator will assess the causal relationship between the investigational product and each AE, and answer yes or no to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as yes.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study staff: "Have you had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol-mandated safety assessments will be summarised in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated safety result will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a subject shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥3 x upper limit of normal (ULN) **or** total bilirubin ≥2 x ULN may need to be reported as SAEs, please refer to Appendix D, Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law, for further instructions.

6.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then the investigator or other study centre staff should inform the appropriate AstraZeneca representatives within 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. The investigator or other study centre staff should inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in Table 2. The safety samples will be analysed by the laboratory at the study centre. The date and time of sample collection will be recorded in the CRF.

The safety laboratory variables to be measured are provided in Table 4.

Table 4 Safety laboratory variables

Clinical chemistry (serum)	Haematology (blood)
Albumin	Haemoglobin
Alkaline phosphatase	Leukocytes
Aspartate aminotransferase	Absolute leukocyte differential count
Alanine aminotransferase	Platelet count
Total bilirubin	
Total calcium	**Urinalysis**
Creatinine	Glucose
Glucose	Haemoglobin
Potassium	Protein
Sodium	

Serology	Other
Human immunodeficiency virus[a]	Follicle-stimulating hormone (females only)[a]
Hepatitis B and C[a]	Luteinising hormone (females only)[a]
	Pregnancy test (females only)
	Creatinine clearance

[a] At screening only.

The healthy volunteers in Group 2 will fast for 4 hours prior to the safety laboratory assessments at screening and during the residential period. Fasting is not required for the follow-up visit.

Luteinising hormone and FSH will be measured in females to determine menopausal status. A serum pregnancy test will be performed for females at screening, Day -1, and follow-up.

Urine will be tested for the following drugs of abuse at screening and Day -1: amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, morphine, tetrahydrocannabinol, and opiates. Subjects will be screened for alcohol at screening and Day -1. If a subject tests positive for any of these screening tests, he/she will be excluded from the study.

A urine sample for urinalysis and microscopy will be collected, if possible, together with other clinical laboratory evaluations.

Creatinine clearance will be estimated using the Cockroft-Gault formula at screening, admission, and discharge:

$$Males:\ CrCL(mL/\min) = \frac{(140 - age) \times (kg\ body\ weight)}{(0.814 \times micromol/L\ serum\ creatinine)}$$

$$Females:\ CrCL(mL/\min) = \frac{(140 - age) \times (kg\ body\ weight) \times 0.85}{(0.814 \times micromol/L\ serum\ creatinine)}$$

where age is expressed in years, weight in kg, and serum creatinine in µmol/L.

Laboratory values outside the reference ranges suspected to be of any clinical significance will be repeated (eg, ALT >2 x ULN, 80 U/L [whichever is the lowest], alkaline phosphatase [ALP] >ULN, bilirubin >1.5 x ULN, 38 µmol/L [whichever is the lowest]). Subjects in whom suspected clinical significance is confirmed will either not be included in the study, or if already included will be followed until normalisation or as long as the investigator considers necessary. Additional laboratory variables may be performed for safety reasons if judged appropriate by the investigator.

NB. In case a subject shows an AST **or** ALT ≥3 x ULN **or** total bilirubin ≥2 x ULN please refer to Appendix D, Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law, for further instructions.

For blood volume see Section 7.1.

6.3.6 Physical examination

Physical examinations will be performed at the times indicated in Table 2.

A complete physical examination will include an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, respiratory, and neurological systems.

A brief physical examination will include an assessment of the following: general appearance, skin, head and neck, lymph nodes, abdomen, cardiovascular status, and respiratory system.

Height will be measured in centimetres and weight in kilograms. Measurements should be taken without shoes and the same scale should be used for all measurements. Subjects' BMI will be calculated from the height and weight. Height and weight will be measured at screening, but only weight will be measured on Day -1 and at the follow-up visit.

6.3.7 ECG

The 12-lead ECGs will be performed at the times indicated in Table 2.

6.3.7.1 Resting 12-lead ECG

The 12-lead paper ECGs will be performed after 10 minutes rest in the supine position. Only the overall evaluation (normal/abnormal) will be recorded in the CRF.

6.3.8 Vital signs

Vital signs will be assessed at the times indicated in Table 2.

6.3.8.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured after 10 minutes rest in the supine position using. If possible, the same arm and the same make and model of equipment should be used for each evaluation. During the residential period, predose blood pressure and pulse rate will be evaluated within 60 minutes before the start of the infusion.

6.4 Pharmacokinetics

For all groups and periods, the date and time of the infusion start and stop, as well as start/stop of any infusion interruptions and restart of the infusion, and the actual volume and amount of ceftaroline fosamil infused will be recorded.

6.4.1 Collection of samples

Blood samples (approximately 4 mL per sample) for determination of ceftaroline fosamil (the prodrug of ceftaroline), ceftaroline, and ceftaroline M-1 (the metabolite of ceftaroline) concentrations in plasma will be taken contralaterally from the dosing arm at the times presented in the study plans, Figure 3, and Figure 4. The date and time of collection of each blood sample will be recorded. In addition, for Group 1/Period 2 only, the sampling location (predialyser or postdialyser) will be recorded for all blood samples collected during and surrounding the haemodialysis session.

In Group 1/Period 2 only, blood samples will be taken at specified time points for haematocrit and endogenous markers including blood urea nitrogen and creatinine. Dialysate will be collected over 1-hour intervals throughout the entire haemodialysis session (approximately 4 hours). The blood flow, dialysate flow rate, dialysate volume, type of dialysis membrane, and the make and model of the dialyser will be recorded. For each collection interval, the entire dialysate will be collected, its volume and collection start/stop date recorded, and the primary and backup samples retained for analysis of ceftaroline and ceftaroline M-1 concentrations.

Samples will be collected, labelled, stored, and shipped as detailed in Laboratory Manual.

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Samples for determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 concentrations in plasma and of ceftaroline and ceftaroline M-1 in dialysate will be analysed

by using appropriate bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (ie, ceftaroline fosamil, ceftaroline, and ceftaroline M-1) at the time of receipt by the bioanalytical laboratory will be analysed.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is presented in Table 5.

Table 5 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)[a]	No. of samples (Group 1)	No. of samples (Group 2)	Total volume (mL) (Group 1)	Total volume (mL) (Group 2)
Safety	Clinical chemistry	2	6	3	12	6
	Haematology	2	6	3	12	6
	Serology	3.5	1	1	3.5	3.5
Pregnancy test, luteinising hormone, and follicle-stimulating hormone[b]		3.5	3	4	10.5	14
Pharmacokinetics		4	37 (32 +5[c])	14	148	56
Haematocrit (Group 1/ Period 2 only)		2	2	NA	4	NA
Blood urea nitrogen and creatinine (Group 1/Period 2 only)		2	10 (5 + 5[c])	NA	20	NA
Total					**210**	**85.5**

[a] If a cannula is used, an additional 1 mL of blood will be collected to flush the cannula at each sample time point.
[b] Females only.
[c] Samples collected from postdialyser line.

NA: not applicable.

The number of samples collected, as well as the volume required for each analysis may be changed during the study. However, the maximum volume to be drawn from each subject will not exceed 450 mL, ie, the same volume as would be drawn during a regular blood donation.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

7.2.1 Safety samples

The safety samples will be disposed of 7 days after analysis.

7.2.2 Pharmacokinetic and/or pharmacodynamic samples

Pharmacokinetic samples will be disposed of after the bioanalytical report finalisation or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses. Samples may also be disposed of earlier, pending further notification.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report.

Additional analysis may be conducted on the biological samples to further investigate the identity of drug metabolites. The biological samples may be retained for a maximum of 2 years following the finalisation of the CSR. Any results from such analyses will be reported separately from the CSR.

7.3 Labelling and shipment of biohazard samples

The principal investigator at will ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C, International Air Transport Association (IATA) 6.2 Guidance Document.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment, and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their lifecycle.

The principal investigator at the study centre will keep full traceability of collected biological samples from the subjects while in storage at the study centre until shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire lifecycle through internal procedures, monitoring of the study centre, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire lifecycle.

7.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As the collection of the biological (PK and safety) samples is an integral part of the study, then the subject is withdrawn from further study participation.

The principal investigator will:

- Ensure subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensure that biological samples from that subject, if stored at the study centre, are immediately identified, disposed of/destroyed, and the action documented
- Ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented, and the signed document returned to the study centre
- Ensure that the subject and AstraZeneca are informed about the sample disposal

AstraZeneca will ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, and the action documented and returned to the study centre.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The informed consent form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final CSP, including the final version of the informed consent form and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable EC and to the study centre's staff.

The opinion of the EC should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The EC should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the informed consent form that are needed to meet local requirements.

If required by local regulations, the CSP should be re-approved by the EC annually.

Before enrolment of any subject into the study, the final CSP, including the final version of the informed consent form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, EC, and principal investigator with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

8.4 Informed consent

The principal investigator will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed informed consent form is stored in the Investigator's Study File

- Ensure a copy of the signed informed consent form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an EC

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the principal investigator and AstraZeneca.

If there are any substantial changes to the CSP, then these changes will be documented in a CSP amendment and where required in a new version of the CSP (revised CSP).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for revised CSPs.

AstraZeneca will distribute any subsequent amendments and new versions of the CSP to the investigator. For distribution to the EC see Section 8.3.

If a CSP amendment requires a change to the study centre's informed consent form, AstraZeneca and the study centre's EC are to approve the revised informed consent form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the EC.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the study centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the CSP, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the study centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

Quintiles will manage this study on behalf of AstraZeneca.

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the study centre to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- Discuss with the investigator (and other staff involved with the study) their responsibilities with regard to CSP adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator

9.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the study centre staff and also train them in any study-specific procedures and system(s) utilised.

The principal investigator will ensure that the appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study centre, including visits to:

- Provide information and support to the investigator
- Confirm that facilities remain acceptable
- Confirm that the study centre staff is adhering to the CSP, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The AstraZeneca representative will be available between visits if the investigator or other staff at the study centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The principal investigator should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this CSP and the Clinical Study Agreement, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the principal investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.4.1 Archiving of study documents

The investigator will follow the principles outlined in the Clinical Study Agreement.

9.5 Study timetable and end of study

The end of the study is defined as "the last visit of the last subject undergoing the study".

The study is expected to start in Q3 2012 and to end by Q1 **2014**.

The study may be terminated at the study centre if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with ceftaroline fosamil.

10. DATA MANAGEMENT

Data management will be performed by Quintiles.

Data will be entered into an electronic data capture (EDC) system. Should an EDC system not be in use for any reason, paper CRFs will be used and the data later entered into the EDC system.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by Quintiles Data Management.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations of the investigational product due to AEs (DAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Clinical Pharmacology Alliance physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of the safety data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

11.2 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analyses of the plasma concentration data for ceftaroline fosamil (the prodrug of ceftaroline), ceftaroline, and ceftaroline M-1 (the metabolite of ceftaroline) and of ceftaroline and ceftaroline M-1 concentrations in dialysate will be performed at Quintiles Inc., Overland Park, Kansas, USA. Quintiles Standard Operating Procedures and Work Instructions will be used as the default methodology if not otherwise specified. The actual sampling times (in unit of hour) will be used in the plasma PK parameter calculations.

Pharmacokinetic parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 5.2, or higher, (Pharsight Corp., Mountain View, California, USA). All PK computations will be performed using WinNonlin® Professional Version 5.2, or higher; or SAS® Version 9.2, or higher (SAS Institute Inc., Cary, North Carolina, USA).

For missing samples or samples collected close to but not exactly at the end of the infusion, ceftaroline fosamil concentrations at the end of infusion will not be imputed unless warranted by the data. If a concentration of ceftaroline fosamil at the end of infusion needs to be estimated, the imputation will be in accordance with procedures described in Quintiles Standard Operating Procedures. The decision to impute a missing end of infusion value will be made on a case-by-case basis and documented in the CSR. In brief, the estimation steps are as follows:

1. Analyse the concentration-time data using an intravenous bolus model by setting the end of infusion time as the dosing time

2. Back-extrapolate the concentration at the time of dosing (ie, the end of infusion concentration)

3. Augment the original concentration-time data set by inserting the back-extrapolated end of infusion concentration

4. Process the augmented data set with an intravenous infusion model

Any imputed values for ceftaroline fosamil will solely be used for PK parameter calculations and will not be included in any summary or inferential statistics. Imputed values will be reported in the CSR. Imputations for the end of infusion concentrations will not be performed for ceftaroline and ceftaroline M-1.

Where possible, the PK parameters listed below will be derived. For Group 1/Period 2 samples collected during the haemodialysis, only predialyser concentrations will be included in the analyses, unless otherwise indicated. Other parameters may also be calculated if deemed appropriate. The molecular weights to be applied in the PK calculations are 684.7 for ceftaroline fosamil, 604.7 for ceftaroline, and 622.7 for ceftaroline M-1.

The following plasma PK parameters will be determined for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in Group 1 (both Periods 1 and 2) and Group 2:

- Maximum plasma concentration (C_{max}, µg/mL)

- Time to maximum concentration (t_{max}, h)

- Area under the plasma concentration-time curve from zero to infinity (AUC, µg•h/mL)

- Area under the plasma concentration-time curve from zero (ie, start of infusion) to time of the last quantifiable concentration ($AUC_{(0-t)}$, µg•h/mL)

- Area under the plasma concentration-time curve from zero to 12 hours after the start of the infusion ($AUC_{(0-12)}$, µg•h/mL)

- Terminal rate constant (λ_z, 1/h)
- Terminal half-life ($t_{1/2\lambda z}$, h), determined as $\ln(2)/\lambda_z$
- Dose-normalised C_{max}, AUC, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}12)}$
- C_{max} ratio of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline (MR_{Cmax}) (adjusted for differences in molecular weights)
- AUC ratios of ceftaroline M-1/ceftaroline (MR_{AUC}) (adjusted for differences in molecular weights)

In addition, the following plasma PK parameters will be calculated for ceftaroline and ceftaroline fosamil in Group 1 (both Periods 1 and 2) and Group 2:

- Mean residence time (MRT, h)
- Total body clearance of drug from plasma (CL for ceftaroline fosamil, apparent CL for ceftaroline [L/h])
- Volume of distribution based on the terminal phase (V_z for ceftaroline fosamil, apparent V_z for ceftaroline [L])
- Volume of distribution at steady-state (V_{ss} for ceftaroline fosamil, apparent V_{ss} for ceftaroline [L])

The following parameters will be calculated for ceftaroline and ceftaroline M-1, unless otherwise noted, in Group 1 Period 2 only:

- Area under the plasma concentration-time curve from 75 minutes to 5.25 hours after the start of the infusion ($AUC_{(1\text{-}5)}$, µg•h/mL)
- Amount of drug extracted unchanged into the dialysate (A_D, mg) during each 1-hour interval, cumulatively, and overall ($A_{D(1\text{-}5)}$, mg) for the entire haemodialysis session (time: 75 minutes to 5.25 hours after the start of infusion)
- Percent of dose recovered in dialysate (f_D,%) during each 1-hour interval, cumulatively, and overall ($f_{D(1\text{-}5)}$,%) for the entire haemodialysis session (time: 75 minutes to 5.25 hours after the start of infusion); adjusted for the molecular weight differences as follows:

  – Ceftaroline

  $f_D,\% = 100 \times (A_D/[Dose*604.7/684.7])$ or

  $f_{D(1\text{-}5)},\% = 100 \times (A_{D(1\text{-}5)}/[Dose*604.7/684.7])$

– Ceftaroline M-1

f_D,% = 100 x (A_D /[Dose*622.7/684.7]) or

$f_{D(1-5)}$,% = 100 x ($A_{D(1-5)}$ /[Dose*622.7/684.7])

- Extraction coefficient (E) at each time point during haemodialysis will be calculated for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 as follows:

  $(C_a - C_v)/C_a$

  where, C_a and C_v are the predialyser and postdialyser plasma concentrations, respectively.

  In addition, E will be calculated for the endogenous markers blood urea nitrogen and creatinine.

- Haemodialysis clearance (CL_D, L/h) of ceftaroline and ceftaroline M-1 will be calculated from both recovery data (primary method) as well as based on Fick principle (secondary method):

  – 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.

The following PK parameters of each analyte will be calculated for diagnostic purposes and listed but not summarised for plasma data in all groups and periods:

- The time interval (λ_z upper and lower) of the log-linear regression to determine λ_z
- Number of data points (λ_z, N) included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used
- Coefficient of determination for calculation of λ_z (Rsq). If Rsq is 0.80 or less, λ_z and related parameters will not be reported
- The percent of AUC which is extrapolated to infinity (%AUC_{ex}). If the extrapolated area (C_{last}/λ_z) is greater than 20% of AUC, then AUC and related parameters will be not reported

The linear up/log down trapezoidal summation method will be used for calculation of all areas under the curve.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety and PK, respectively.

12.1 Description of analysis sets

12.1.1 Safety analysis set

All subjects who received at least 1 dose of investigational product, and for whom any postdose data are available will be included in the safety population.

12.1.2 Pharmacokinetic analysis set

The PK analysis set will include all subjects who received at least 1 dose of ceftaroline fosamil and have at least 1 measured concentration of any of the 3 analytes in plasma or dialysate at a scheduled time point after the start of the infusion. The PK analysis set should include all evaluable data appropriate for the evaluation of interest (with no major protocol deviations, violations, or events thought to significantly affect the PK of the investigational product) from all subjects who receive investigational product.

12.2 Methods of statistical analyses

12.2.1 General principles

The PK and safety summaries, individual figures, and data listings as well as the statistical analysis of PK variables will be the responsibility of the study biostatistician at Quintiles Inc., Overland Park, Kansas, USA (using SAS® Version 9.2 or higher and, where appropriate, additional validated software). Graphics may be prepared with SAS® Version 9.2, or higher; or SigmaPlot® 9.0, or higher (Systat Software Inc., San Jose, California, USA).

Data will generally be listed and summarised by renal function group (and further stratified by period for ESRD patients). Continuous variables will be 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}) will also include geometric mean and geometric coefficient of variation (CV%). Means, SD, and CV% will not be reported for t_{max}. Pharmacokinetic concentration data will also include lower and upper SD bounds which are defined as exp(m±s) where m and s are the mean and SD, respectively, of the natural log-transformed data.

The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale.

Categorical variables will be summarised in frequency tables (frequency and proportion) by renal function group.

In general, Quintiles Global Standard Operating Procedures will be followed.

Baseline characteristics will be summarised across all subjects.

12.2.2 Safety

All safety data (scheduled and unscheduled) will be presented in the data listings.

Safety variables (ie, clinical laboratory values and vital signs) will be reported to the same precision as the source data. Derived variables will be reported using similar precision to those from which they were derived.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in data listings. All AEs and clinical laboratory outliers that occur following the first dose of investigational product will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations.

The ECG data will only be listed.

All available data from subjects in the safety analysis set will be included in the safety analyses. No adjustment or imputation will be utilised for missing values or for subjects who withdraw prior to completing the study, neither will analyses be restricted to subjects with complete data.

All SAEs will be collected for each subject from when informed consent is obtained until the follow-up visit. All AEs will be collected from Day 1 until the follow-up visit. Adverse events that occur before dosing will be reported separately.

The AEs will be summarised by Preferred Term and System Organ Class using MedDRA vocabulary (version 12.0 or higher) by renal function group and across all renal function groups. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of subjects who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarised.

12.2.3 Pharmacokinetic analyses

Individual PK blood and dialysate sample collection times, as well as derived sampling time deviations, and concentration-time data will be listed.

Pharmacokinetic data will be presented by analyte, renal function group, and period, as appropriate.

Plasma concentrations will be summarised by nominal time points using descriptive statistics.

Plasma concentrations that are below the lower limit of quantification (LLOQ) will be handled as follows:

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated
- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean, and CV% will be set to Not determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for SD and CV% and BLQ will be written in fields for mean, geometric mean, minimum, median, and maximum
- The number of BLQ values (n below LLOQ) will be reported for each time point

Individual plasma concentration-time profiles of the analytes will be depicted on linear and semi-logarithmic scales, showing all analytes on a single plot for each patient, and also for all patients on a single plot for each analyte. Geometric mean plasma concentration-time profiles (with lower/upper SD bounds as defined in Section 12.2.1) of each analyte will be depicted on linear and semi-logarithmic scales. For Group 1 Period 2, the full concentration-time profiles will include predialyser concentrations collected during haemodialysis and concentrations from other time points while postdialyser concentrations will be plotted separately.

Plasma and dialysate PK parameters will be summarised by analyte, renal function group, and period, as appropriate, using descriptive statistics. Figures of observed and dose-normalised C_{max}, AUC, and $AUC_{(0-t)}$ will be presented by analyte for visual comparisons of systemic exposures in healthy volunteers and in ESRD patients under nondialysis and dialysis conditions. Additional plots may be produced for graphical presentations of data as deemed appropriate.

12.3 Determination of sample size

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. A sample size of 6 subjects is considered sufficient to characterise the PK of each dose. The study will recruit 8 subjects per group as a contingency against dropouts.

12.4 Data monitoring committee (Not applicable)

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The principal investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4.**

In the case of a medical emergency the investigator may contact the Clinical Pharmacology Alliance physician. If the Clinical Pharmacology Alliance physician is not available, contact the Clinical Pharmacology Alliance Programme Director at the AstraZeneca.

Name	Role in the study	Address & telephone number

13.2 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module
- An overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose on an AstraZeneca investigational product occurs in the course of the study, then the investigator or other study centre staff will inform appropriate AstraZeneca representatives **within 1 day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

No specific information is available on the treatment of an overdose with ceftaroline. There were no reports of an acute overdose of ceftaroline in clinical studies. In the event of an acute overdose, ceftaroline should be discontinued and general supportive treatment administered. Ceftaroline can be removed by haemodialysis. In patients with ESRD administered 400 mg of ceftaroline fosamil, the mean total recovery of ceftaroline in the dialysate following a 4-hour haemodialysis session started 4 hours postdose was 76.5 mg (21.6% of the dose). However, no information is available on the use of haemodialysis to treat an overdose of ceftaroline.

For overdoses associated with an SAE, standard reporting timelines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other study centre staff should inform appropriate AstraZeneca representatives **within 1 day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.4, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months following the last investigational product administration.

Pregnancy of the subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should if possible be followed up and documented.

14. LIST OF REFERENCES

FDA Guidance for Industry 2010
FDA Guidance for Industry: Pharmacokinetics in subjects with impaired renal function: study design, data analysis, and impact on dosing and labelling. United States Department of Health and Human Services, FDA, Centre for Drug Evaluation and Research, Centre for Biologics Evaluation and Research. March 2010.

CHMP Note for Guidance 2004
CHMP Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Renal Function. Committee for Medicinal Products for Human Use. 23 June 2004.

Clinical Study Protocol Appendix B

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00012
Edition Number	1

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00012
Edition Number	1

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

CONTENTS

1. INTRODUCTION

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's law (PHL) criteria at any point during the study.

The investigator participate, together with AstraZeneca (AZ) clinical project representatives in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) decisive factors are fulfilled, indicating a Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP). HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than the IMP.

The Investigator fulfils requirements for the recording of data pertaining to PHL/Hy's law (HL) cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

For the purpose of this process definitions are as follows

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) **and** total bilirubin (TBL) ≥2 x ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)
Aspartate aminotransferase or ALT ≥3 x ULN **and** TBL ≥2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug.' The elevations do not have to occur at the same time or within a specified time frame.

3. ACTIONS REQUIRED IN CASES OF ALT ≥3 X ULN, AST ≥3 X ULN OR TBL ≥2 X ULN

3.1 Identification and determination

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following criteria in isolation or in combination:

- ALT ≥3 x ULN
- AST ≥3 x ULN
- TBL ≥2 x ULN

Please follow the instructions below.

- Without delay review each new laboratory report and if a subject has ALT ≥3 x ULN, AST ≥3 x ULN **or** TBL ≥2 x ULN at any visit, in isolation or in combination:
  - Notify the AstraZeneca representative
  - Promptly enter the laboratory data into the laboratory CRF
  - Review laboratory reports from all previous visits
- Determine whether the subject meets PHL (see Section 2 of this Appendix)

3.2 Follow-up

3.2.1 Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria (see section 2 of this Appendix):

- Inform the AZ representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

3.2.2 Potential Hy's Law Criteria met

If the subject meets PHL criteria (see section 2 of this Appendix):

- Notify the AZ representative who will then inform the central Study Team (ST)

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data.

The Investigator:

- Follows the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigates the etiology of the event and perform diagnostic investigations as discussed with the SP
- Completes the 3 Liver eCRF Modules as information becomes available
- If at any time (in consultation with the SP) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

3.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the SP contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP. The AZ Medical Science Director (MSD) and Global Safety Physician (GSP) will also be involved in this review together with other subject matter experts as appropriate. According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the ALT or AST **and** TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation **is** an AE/SAE, record the AE/SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST **and** TBL elevations other than the IMP:

- Report an SAE (report term ‘Hy’s Law’) according to AZ standard processes.
  - The ‘Medically Important’ serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

4. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm