AstraZeneca

PROTOCOL SYNOPSIS

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

Study centre and number of subjects planned

Approximately 40 healthy male and female subjects will be randomised.

Study period		Phase of development
Estimated date of first subject enrolled	Q2 2012	Clinical Pharmacology (Phase I)
Estimated date of last subject completed	Q4 2012	

Objectives

Primary objectives

- To investigate the safety and tolerability of single and multiple intravenous infusions of different dose regimens of ceftaroline fosamil as compared to placebo in healthy male and female subjects

Secondary objective

- To characterise the pharmacokinetics of ceftaroline, ceftaroline fosamil (the prodrug of ceftaroline), and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) in plasma and urine following single- and multiple-dose administrations of different ceftaroline fosamil intravenous infusion regimens in healthy male and female subjects

Exploratory objective

- To collect and store blood samples for potential future exploratory research aimed at exploring biomarkers involved in the pharmacokinetics, pharmacodynamics, safety, tolerability, and efficacy of ceftaroline fosamil

These data will not form part of the main report for this study.

Study design

This is a Phase I randomised, double-blind, placebo-controlled, parallel group study in a single study centre to assess the safety, tolerability, and pharmacokinetics of ceftaroline fosamil administered in healthy subjects.

Approximately 40 healthy male and female subjects will be enrolled in 2 cohorts (Cohort 1 and Cohort 2) 20 subjects per cohort with 15 receiving ceftaroline and 5 receiving placebo. Cohort 1 will receive a single intravenous infusion on Day 1 and Day 8 with 2 daily infusions (12 hourly) on Days 2-7, infused over 1 hour. Cohort 2 will receive single intravenous infusion on Day 1 and Day 8 with 3 daily infusions (8 hourly) on Days 2-7 hours, infused over 2 hours.

Target subject population

Approximately 40 healthy male and female subjects aged 18 to 55 years (inclusive) will be divided into 2 cohorts of 20 subjects each to ensure that 12 of the 15 subjects treated with ceftaroline fosamil complete each cohort.

Investigational product, dosage and mode of administration

Multiple intravenous infusions of ceftaroline fosamil starting with a single infusion of 600 mg on Day 1 followed by multiple daily infusions Days 2 to 7, with a single 600 mg infusion on the morning of Day 8.

Cohort 1 will receive a single intravenous infusion on Day 1 and Day 8 with 2 daily infusions (12 hourly) on Days 2-7, infused over 1 hour.

Cohort 2 will receive single intravenous infusion on Day 1 and Day 8 with 3 daily infusions (8 hourly) on Days 2-7 hours, infused over 2 hours.

Comparator, dosage and mode of administration

Placebo to match ceftaroline fosamil.

Duration of treatment

Subjects will be screened for eligibility between Days -28 and -2 and admitted to the study centre on Day -1.

Each subject will receive a single dose of ceftaroline fosamil or placebo on Day 1. Repeated infusions will commence on Day 2 with ceftaroline fosamil or placebo every 12 hours

(Cohort 1) or every 8 hours (Cohort 2). A single infusion will be administered on the morning of Day 8.

Subjects will be discharged from the study centre on Day 9 and return to the study centre for follow-up 7 to 10 days after discharge.

Outcome variable(s):

- Safety (primary)

  Adverse events, laboratory variables, vital signs, electrocardiogram, and physical examination

- Pharmacokinetics

  Where possible, the following plasma and urine pharmacokinetic parameters will be determined for ceftaroline fosamil (the prodrug of ceftaroline), ceftaroline, and ceftaroline M-1, unless otherwise noted. Other pharmacokinetic parameters may also be calculated if deemed appropriate.

  Following the single-dose on Day 1:

- The following plasma pharmacokinetic parameters of all 3 analytes on Day 1 will be calculated: 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 concentrations [$AUC_{(0-t)}$]; area under the plasma concentration-time curve from zero to 12 hours after the start of the infusion [$AUC_{(0-12)}$, to be calculated only for Cohort1], area under the plasma concentration-time curve from zero to 8 hours after the start of the infusion [$AUC_{(0-8)}$, to be calculated only for Cohort 2], apparent terminal rate constant (λ_z), terminal half-life ($t_{1/2\lambda z}$, h), metabolite/parent C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,Cmax}$) and metabolite/ parent AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,AUC}$).

  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), and volume of distribution at steady state (V_{ss} for ceftaroline fosamil, apparent V_{ss} for ceftaroline).

  The following urine pharmacokinetic parameters on Day 1 will be calculated for all 3 analytes: amount of analyte excreted in the urine (A_e) during each interval and cumulatively, fraction of dose excreted into urine ($f_{e,}$%) during each interval and

cumulatively, total fraction of dose excreted in urine for all analytes combined ($f_{e,total}$,%), and renal clearance (CL_R).

Following the multiple dosing on days 4 and 8:

- The following plasma pharmacokinetic parameters of all 3 analytes will be calculated for Day 4 and Day 8: maximum plasma concentration at steady state during dosing interval ($C_{ss,max}$), time to maximum concentration at steady state during dosing interval ($t_{ss,max}$), minimum plasma concentration at steady state during dosing interval ($C_{ss,min}$), area under the plasma concentration-time curve from zero to time of the last quantifiable concentrations [$AUC_{(0-t)}$], area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_τ); average plasma concentration during the dosing interval ($C_{ss,av}$), fluctuation index (FI, %); metabolite/parent C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,Cmax}$); metabolite/ parent AUC_τ ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,AUC}$); apparent terminal rate constant (λ_z), terminal half-life ($t_{½\lambda z}$, h), accumulation ratio based on C_{max} [$R_{ac(Cmax)}$], accumulation ratio based on AUC [$R_{ac(AUC)}$], and linearity factor.

  In addition, the following plasma pharmacokinetic parameters of ceftaroline and ceftaroline fosamil will be calculated for Day 4 and Day 8: mean residence time (MRT), plasma clearance at steady state (CL_{ss} for ceftaroline fosamil, apparent CL_{ss} for ceftaroline), volume of distribution based on the terminal phase (V_z for ceftaroline fosamil, apparent V_z for ceftaroline), and volume of distribution at steady state (V_{ss} for ceftaroline fosamil, apparent V_{ss} for ceftaroline).

  The following urine pharmacokinetic parameters will be calculated for Day 8: amount of analyte excreted in the urine ($A_{e,ss}$, mg) during each interval and cumulatively up to the end of the dosing interval, fraction of dose excreted into urine ($f_{e,ss,}$%) during each interval and cumulatively up to the end of the dosing interval, total fraction of dose excreted in urine for all analytes combined ($f_{e,ss,total-,}$%), and renal clearance ($CL_{R,ss}$, L/h).

Statistical methods

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. A sample size of 12 subjects is considered sufficient to characterise the pharmacokinetics, safety, and tolerability of each dose in healthy subjects.

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

The pharmacokinetics of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 will be evaluated by assessment of concentrations in plasma and urine and calculation of pharmacokinetic parameters. Pharmacokinetic data will be summarised descriptively

including tables, listings, and graphs, as appropriate. Time to steady state will be evaluated by graphical assessments.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
A_e	Amount of analyte excreted in the urine
AE	Adverse event (see definition in Section 6.3.2)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from zero to time of the last quantifiable concentrations
$AUC_{(0-12)}$	Area under the plasma concentration-time curve from zero to 12 hours after the start of the infusion
$AUC_{(0-8)}$	Area under the plasma concentration-time curve from zero to 8 hours after the start of the infusion
AUC_{ex}, %	Percent of AUC which is extrapolated to infinity
AUC_{τ}	Area under the plasma concentration-time curve from zero to the end of the dosing interval
BCRP	Breast cancer resistance protein
BLQ	Below the lower limit of quantification
BMI	Body mass index
CABP	Community-acquired bacterial pneumonia
CL	Total body clearance of drug from plasma
CL_R	Renal clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CPA	Clinical Pharmacology Alliance
CrCl	Creatinine clearance
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
$C_{ss,av}$	Average plasma concentration during the dosing interval
$C_{ss,min}$	Minimum plasma concentration at steady state during dosing interval

Abbreviation or special term	Explanation
cSSSI	Complicated skin and skin structure infection
CV%	Geometric coefficient of variation
CYP	Cytochrome P450
EC	Ethics Committee
ECG	Electrocardiogram
f_e	Fraction of dose excreted into urine
$f_{e,total}$,%	Total fraction of dose excreted in urine
FI, %	Fluctuation index
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GRand	Global randomisation system
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
INR	International normalised ratio
IV	Intravenous
λ_z	Apparent terminal rate constant
LH	Luitenising hormone
LLOQ	Lower limit of quantification
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
min	Minimum
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRT	Mean residence time
n	N for sample size and n for available data
NA	Not applicable
ND	Not Determined
NDA	New Drug Application
OAE	Other Significant Adverse Event (see definition in Section 10.1.1)

Abbreviation or special term	Explanation
OAT	Organic anion transporter
OCT	Organic cation transporter
P-gp	P-glycoprotein
PBP	Penicillin-binding protein
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
q8h	Every 8 hours
q12h	Every 12 hours
$R_{ac(AUC)}$	Accumulation ratio based on AUC
$R_{ac(Cmax)}$	Accumulation ratio based on C_{max}
$R_{M/D,AUC}$	Metabolite/ parent AUC (or AUC_{τ})ratio
$R_{M/D,Cmax}$	Metabolite/ parent C_{max} ratio
Rsq	Goodness of fit statistic for calculation of the apparent terminal rate constant
SAE	Serious adverse event (see definition in Section 6.3.3).
S_{Cr}	Serum creatinine
SD	Standard deviation
SOC	System Organ Class
ss	Steady state
t_{max}	Time to maximum concentration
$t_{1/2\lambda z}$	Terminal half-life
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
USA	United States of America
V_z	Volume of distribution based on the terminal phase
V_{ss}	Volume of distribution at steady state

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 in December 2009 for the treatment of complicated skin and skin structure infections (cSSSIs) and community-aquired bacterial pneumonia (CABP) in adults. This NDA was approved in October 2010 and ceftaroline fosamil is marketed in the USA under the brand name Teflaro™. AstraZeneca submitted a Marketing Authorisation Application of ceftaroline fosamil in the European Union in December 2010 and the application is under review.

1.1 Background

Pre-clinical 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 programme assessed the central nervous system (CNS), cardiovascular, renal, and respiratory effects of ceftaroline fosamil and ceftaroline in vitro and single dose in vivo studies in the rat and monkey. Consistent with the cephalosporin class, convulsions were the main safety finding in the safety pharmacology programme. 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 seen in patients.

Non-clinical 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 the 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 administrations of [^{14}C] ceftaroline fosamil for 14 days in rats, the highest concentration of radioactivity was detected in the kidney followed by skin and radioactivity concentrations in other tissues were lower than those in plasma.

Following a single intravenous dose of [^{14}C] ceftaroline fosamil in rats and monkeys, the dose was excreted in urine predominantly as ceftaroline and its open-ring metabolite ceftaroline M-1. Only a 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. Additional minor metabolites seen 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 the clinical development programme, ceftaroline has been evaluated in healthy adult, elderly, and adolescent subjects, and in subjects with mild to severe renal impairment, as well as in subjects with end-stage renal disease requiring haemodialysis. The safety and efficacy of ceftaroline treatment has been demonstrated in subjects with cSSSIs and in subjects with moderate to severe CABP.

The clinical development programme for ceftaroline fosamil comprise 17 clinical studies, including 2 Phase III cSSSI studies and 2 Phase III CABP safety and efficacy studies. Approximately 1700 subjects have received ceftaroline fosamil as a part of this programme. At the recommended dose regimen of 600 mg ceftaroline fosamil administered as a 1-hour intravenous infusion administered 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 that was compatible with treatment of cSSSI and CABP and known cephalosporin class effects. A reduced dose of 400 mg ceftaroline fosamil infused over 1 hour every 12 hours is recommended for subjects with moderate renal impairment, defined as a creatinine clearance (CrCl) of 30 mL/min < CrCl ≤50 mL/min.

The incidences of treatment-emergent adverse events (TEAEs) experienced by subjects receiving ceftaroline fosamil were similar compared with those experienced by subjects receiving 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 receiving 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 appears 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 therapy. Cephalosporins are known to be associated with positive direct Coombs' test results. Although rates of sero-conversion 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 therapies and resulted in similar numbers of subjects prematurely discontinued from investigational product administration 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 dose levels of ceftaroline fosamil studied (600 mg intravenously every 12 hours or 400 mg intravenously every 12 hours); ceftaroline demonstrated an acceptable safety profile that was compatible with treatment of cSSSIs 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, thorough QTc study). Multiple total doses of 1800 mg/day have been assessed in 3 healthy subjects studies: 600 mg administered every 8 hours as 1-hour infusions were assessed over 10 days in P903-020 (8 subjects); 600 mg administered every 8 hours as 1-hour infusions were assessed over 10 days in Study CXL-PK-01 (8 subjects); 900 mg administered every 12 hours as 1-hour infusions were assessed over 10 days in Study CXL-PK-01 (9 subjects). In Study CXL-PK-01, ceftaroline fosamil was studied in combination with equal doses of the β-lactamase inhibitor NXL104. The safety profile of ceftaroline fosamil in the subjects in these high dose studies was similar to that observed in the overall population exposed to ceftaroline.

The cumulative clinical experience with ceftaroline identified the adverse reactions is presented in Table 1.

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

System Organ Class	Adverse events
Blood and lymphatic disorders	Thrombocytopenia, anaemia
Nervous system disorders	Headache, dizziness
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Rash, pruritis, 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, positive direct Coombs'
General disorders and administrative site conditions	Infusion site reactions, erythema, pain, phlebitis, pyrexia

This information is detailed in Table 10-1 of the Investigator's Brochure.

The following is a summary of the basic pharmacokinetic (PK) properties of ceftaroline (following intravenous infusions 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 of 2 to 3 hours
- The prodrug ceftaroline fosamil is rapidly converted to active ceftaroline in plasma by phosphatases. Ceftaroline is further metabolised via opening of the β-lactam ring to form the microbiologically inactive metabolite M-1 and additional minor 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 [GFR])
- 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

For further information, refer to the Investigator Brochure.

1.2 Rationale for conducting this study

Ceftaroline fosamil for injection (ceftaroline) is being developed for the treatment of serious bacterial infections including those caused by aerobic gram-negative and gram-positive pathogens. During the first clinical study (P903-01), ceftaroline was considered to be safe and well tolerated in all subjects at single doses up to 1000 mg and multiple doses of 600 mg every 12 hours for 14 days, or 800 mg every 24 hours for 7 days. Based on these safety data, additional Phase I, II, and III studies have been completed or will be conducted using ceftaroline fosamil at 600 mg every 12 hours (infused over 1 hour) or 600 mg every 8 hours (infused over 2 hours). Given the established safety of ceftaroline, the current study will investigate 2 dose regimens, 600 mg administered every 12 hours (infused over 1 hour) and 600 mg every 8 hours (infused over 2 hours), in healthy male and female subjects. The aim of the study is to characterise the safety and PK profile of ceftaroline with longer infusions of ceftaroline fosamil at potentially high dose therapeutic regimens.

The highest total daily dose (1800 mg ceftaroline fosamil) in this study is chosen to be higher than the approved ceftaroline fosamil dose in the USA (1200 mg administered intravenously as 600 mg every 12 hours, infused over 1 hour), in order to optimise the coverage for methicillin-resistant *Staphylococcus aureus* (MRSA). As cephalosporin concentration is critical to therapeutic success, this study will explore a dose regimen of ceftaroline fosamil that has not been extensively studied before. To date, 2000 mg of ceftaroline fosamil has been the maximum single dose and 600 mg 1-hour infusion every 8 hours (with a daily total of 1800 mg) has been the highest daily dose on repeated infusions. The current study will evaluate the high multiple-dose regimen of 600 mg every 8 hours with the doses being infused over a longer duration of 2 hours. The time above minimum inhibitory concentrations (MIC) is influenced by the shape of the concentration-time profiles and the thresholds of MIC. In comparison to the 600 mg 1-hour infusions, albeit the decrease in the infusion rate and hence lower concentrations at corresponding time points during the infusion, post-infusion concentrations following the 2-hour infusion at corresponding time points relative to the start of the infusion will be higher due to longer infusion time. The net effect of this high-dose longer-duration regimen is expected to increase the time above the targeted MICs, and improving the chance of therapeutic success in pathogens with MICs >1 mg/L. In light of this, a proper evaluation of the 600 mg every 8 hours administered over 2 hours versus the approved 600 mg every 12 hours administered over 1 hour regimen with respect to safety, tolerability, and PK is needed. Results of this study will support administrations in the Phase III program.

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 was 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 the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) 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 EU PRMP, 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.

There is a tremendous need to develop new treatments for severe infection. The benefit of the present study is that it will provide invaluable human data of safety and PK with high doses of ceftaroline fosamil given in multiple doses. These data will be critical for further development of this compound. Careful screening, monitoring, and adherence to a plan of intervention for adverse clinical signs will be performed during the conduct of this clinical investigation.

2. STUDY OBJECTIVES

2.1 Primary objectives

- To investigate the safety and tolerability of single and multiple intravenous infusions of different dose regimens of ceftaroline fosamil as compared to placebo in healthy male and female subjects

2.2 Secondary objective

- To characterise the PK of ceftaroline, ceftaroline fosamil (the prodrug of ceftaroline), and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) in plasma and urine following single- and multiple-dose administrations of different ceftaroline fosamil intravenous infusion regimens in healthy male and female subjects

2.3 Exploratory objective

- To collect and store blood samples for potential future exploratory research aimed at exploring biomarkers involved in the PK, pharmacodynamics (PD), safety, tolerability, and efficacy of ceftaroline fosamil

These data will not form part of the main report for this study.

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 a Phase I, randomised, double-blind, placebo-controlled, parallel group study in healthy male and female subjects conducted at a single study centre. Up to 40 healthy subjects aged 18 to 55 years (inclusive) will participate in 2 cohorts. Each cohort will be divided into 4 subgroups of 5 subjects each.

Twenty subjects will participate in each cohort and will receive either ceftaroline fosamil (15 subjects) or placebo (5 subjects). Each subject will only participate in 1 cohort. The dose will be 600 mg 12-hourly (infused over 1 hour) in Cohort 1 and 600 mg 8-hourly (infused over 2 hours) in Cohort 2.

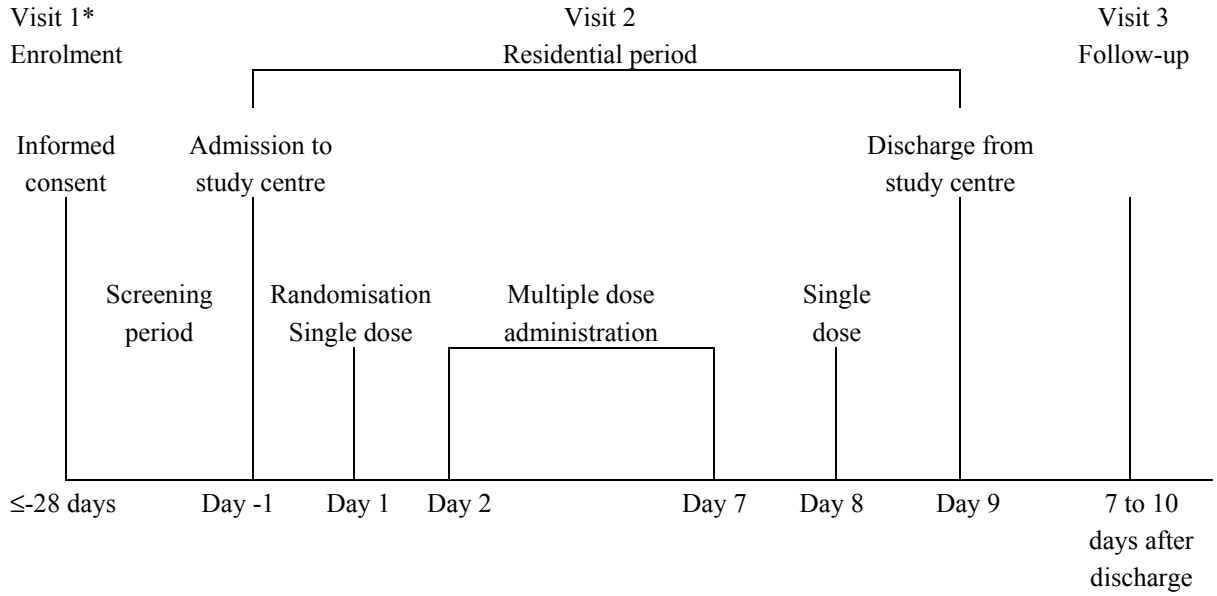
After a screening period of up to 28 days, subjects will be admitted to the study centre on Day -1, discharged on Day 9 and followed up 7 to 10 days after discharge (see Figure 1).

On Days 1 and 8 subjects will receive a single dose of 600 mg ceftaroline fosamil or placebo.

Repeated infusions will commence on Day 2. Subjects will then receive ceftaroline fosamil or placebo every 12 hours (Cohort 1) or every 8 hours (Cohort 2) from Days 2 to 7. It is anticipated that this will be sufficient to achieve and maintain steady state for several days and evaluate the safety of multiple infusions adequate for the intended target. Throughout the residential period there will be safety monitoring and serial blood samples for PK evaluation (for details see Figure 3).

Local tolerability will be assessed according to the VIP scale. The VIP score will be recorded for all local reactions; any local reaction with a VIP score of 2 or greater will be determined as an ISR and will be recorded as an adverse event. See Section 6.3.1.

Figure 1 Study flow chart



* Visit 1 may be conducted over 1 or more days during the screening period.

Figure 2 Study plan

Visit number	1 Screening Period	2 Residential Period									Discharge	3 Follow-up	
Activity/Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**7 to 10 days after last dose**	**Details in Section**
Informed consent[a]	X												8.4
Demography	X												6.2
Medical/surgical history	X												6.2
Inclusion/exclusion criteria	X	X											4.1 and 4.2
Physical examination	X	X					X[f]				X	X[f]	6.3.7
Height, weight, and BMI	X											X[b]	6.3.7
Admission		X											
Vital signs (blood pressure and pulse rate)[g]	X	X	X	X	X			X			X	X	6.3.9
Haematology, clinical chemistry, and urinalysis[c]	X	X					X				X	X	6.3.6
Local tolerability measurements (infusion site)[h]		X	X	X	X	X	X	X	X	X			6.3.1
Pregnancy test	X	X										X	6.3.6
Luteinising hormone/ follicle-stimulating hormone	X												6.3.6
Estimate creatinine clearance	X										X		6.3.6
Hepatitis B, hepatitis C, and HIV	X												6.3.6

Figure 2 Study plan

Visit number	1 Screening Period	2 Residential Period									Discharge	3 Follow-up	
Activity/Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	7 to 10 days after last dose	Details in Section
Drugs of abuse screen and smokerlyzer test	X	X											6.3.6
Alcohol breath test	X	X											6.3.6
12-lead electrocardiogram	X	X					X				X	X	6.3.8
Exploratory biomarker blood sampling		X[d]										X	6.5.1
Randomisation			X										5.2
Administer investigational product			X	X	X	X	X	X	X	X			5.5.2
PK blood sampling[e]			X	X		X		X		X	X		6.4
PK urine collection[e]			X	X						X	X		6.4
Adverse events			X	X	X	X	X	X	X	X	X	X	6.3
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	6.3
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	5.6
Discharge											X		

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

[a] Informed consent will be collected prior to any procedures being performed.
[b] Only weight will be measured at the follow-up visit.
[c] The subject will fast for at least 4 hours prior to clinical laboratory evaluations at screening and during the residential period. Fasting is not required at the follow-up visit.

[d] On Day -1 or Day 1 pre-dose.

[e] Pharmacokinetic blood samplings and urine collections are detailed in Figure 3.

f Brief physical examination.

g Supine blood pressure and pulse will be evaluated after the volunteer has rested in supine position for at least 10 minutes prior to the evaluation. If possible, the same equipment should be used for each evaluation. It is preferable to avoid the arm with a cannula. While in residence, blood pressure and pulse will be evaluated in the morning prior to dosing on study days 1, 2, 3 and 6

h Pre-dose, immediately after dosing and 1 hour post dose

Figure 3 Pharmacokinetic sampling time points

Study day	Administer investigational product	Protocol time	PK blood sample[c]		PK urine collection[b]
			Cohort 1	Cohort 2	
1		-2 h			X
		Predose[a]	X	X	I
	X	0 (-15 min)			X
		20 min	X		I
		30 min		X	I
		40 min	X		I
		55 min	X		I
		60 min		X	I
		65 min	X		I
		75 min	X		I
		90 min	X	X	I
		115 min		X	I
		120 min	X		X
		125 min		X	I
		2h 15 min		X	I
		2.5 h		X	I
		3 h	X	X	I
		4 h	X	X	X
		6 h	X	X	I

Figure 3 Pharmacokinetic sampling time points

Study day	Administer investigational product	Protocol time	PK blood sample[c]		PK urine collection[b]
			Cohort 1	Cohort 2	
		8 h	X	X	X I
		12 h	X	X	X
		18 h	X	X	I
2		24 h	X	X	X
	X (q12h or q8h)				
3	X (q12h or q8h)				
4		Predose[a]	X	X	
	X (1st dose for q12h or q8h)	0			
		20 min	X		
		30 min		X	
		40 min	X		
		55 min	X		
		60 min		X	
		65 min	X		
		75 min	X		
		90 min	X	X	
		115 min		X	

Figure 3 Pharmacokinetic sampling time points

Study day	Administer investigational product	Protocol time	PK blood sample[c]		PK urine collection[b]
			Cohort 1	Cohort 2	
		120 min	X		
		125 min		X	
		2h 15 min		X	
		2.5 h		X	
		3 h	X	X	
		4 h	X	X	
		6 h	X	X	
		8 h	X	X	
	X (2^{nd} dose for q8h)				
		12 h	X		
	X (2^{nd} dose for q12h)				
	X (3^{rd} dose for q8h)				
5	X (q12h or q8h)				
6		Predose[a]	X	X	
	X (q12h or q8h)				
7	X (q12h or q8h)				
8		-2 h			X

Figure 3 Pharmacokinetic sampling time points

Study day	Administer investigational product	Protocol time	PK blood sample[c]		PK urine collection[b]
			Cohort 1	Cohort 2	
		Predose[a]	X	X	I
	X (final dose in the morning)	0			X I
		20 min	X		I
		30 min		X	I
		40 min	X		I
		55 min	X		I
		60 min		X	I
		65 min	X		I
		75 min	X		I
		90 min	X	X	I
		115 min		X	I
		120 min	X		X
		125 min		X	I
		2 h 15 min		X	I
		2.5 h		X	I
		3 h	X	X	I
		4 h	X	X	X
		6 h	X	X	I

Figure 3 Pharmacokinetic sampling time points

Study day	Administer investigational product	Protocol time	PK blood sample[c]		PK urine collection[b]
			Cohort 1	Cohort 2	
		8 h	X	X	X
		12 h	X	X	X
		18 h	X	X	
		24 h	X	X	X

h hour, min minute, PK pharmacokinetic, q12h every 12 hours, q8h every 8 hours
Cohort 1: 600 mg 1-hour infusion q12h; Cohort 2: 600 mg 2-hour infusion q8h

[a] On Day 1, predose plasma PK samples will be collected within 60 minutes before the start of the infusion. On Days 4, 6, and 8, predose/trough samples will be collected within 15 minutes before the start of the morning infusion.

[b] Subjects will be required to empty their bladders 15 minutes prior to the start of the urine sample collection and will be asked to drink 240 mL of water after bladder emptying. Urine samples will be collected on Day 1 and Day 8 at the following intervals: -2 to 0 hours, 0-2 hours, 2-4 hours, 4-8 hours, 8-12 hours and 12-24 hours.

[C] PK samples times are from the start of the infusion

Additional assessment or sampling times may be added. However, the maximum blood volume taken from each subject will not exceed 450 mL.

3.2 Rationale for study design, doses and control groups

A standard parallel group design is used for this 2 different dose regimen study to evaluate the safety, tolerability, and PK of ceftaroline in healthy subjects. This study is randomised and double-blinded to minimise bias and includes placebo to facilitate the identification of the effects related to the administration of ceftaroline fosamil rather than the study procedures or situations.

The study is conducted in healthy adult subjects to avoid interference from disease process or other drugs. The inclusion and exclusion criteria are defined so that subjects selected for participation in the study are known to be free from other significant illness.

Based on the half-life, it is anticipated that multiple administrations from Day 2 to Day 7 will be sufficient to achieve a steady state.

The requirement of 12 active-dosed subjects to complete the study will aid in reducing the standard error in the estimation of variables such as inter-subject variability in future ceftaroline population PK modeling, and facilitate a comparison of ceftaroline PK between healthy subjects and patients with cSSSI.

The maximum single dose administration was 2000 mg ceftaroline fosamil (infused over 1 hour) with C_{max} and AUC of 106 μg/mL and 248 μg*h/mL, respectively. Ceftaroline demonstrated linear PK up to the administration of 1000 mg dose of ceftaroline fosamil. Since ceftaroline has a short half-life (2 to 3 hours), the administration of 600 mg ceftaroline fosamil as an intravenous infusion over 2 hours every 8 hours is not expected to yield appreciable accumulation, and consequently, the C_{max} and AUC for the repeated administration of 600 mg should remain below that of a single administration of 2000 mg ceftaroline fosamil. In healthy subjects, the predicted C_{max} and AUC of ceftaroline in Cohort 2 after 600 mg 2-hour IV infusion of ceftaroline fosamil every 8 hours, would be 20 μg/mL and 70 μg*h/mL, respectively. In addition, the predicted C_{max} and AUC of ceftaroline in Cohort 1 after 600 mg 1-hour IV infusion of ceftaroline fosamil every 12 hours, would be 25.7 μg/mL and 67.1 μg*h/mL

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, ie, subject screening log, of subjects who entered pre-study screening.

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

4.1 Inclusion criteria

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

1. Provision of signed and dated, written informed consent prior to any study specific procedures including the exploratory biomarker analysis

2. Healthy male and female subjects aged 18 to 55 years (inclusive) with suitable veins for cannulation or repeated venipuncture

3. During the trial, and for 3 months afterwards, men must use a condom and spermicide, and their female partners must use an additional method of contraception (such as oral contraceptives, intrauterine device, cap or diaphragm), unless the subject's partner is post-menopausal or has had a hysterectomy or a bilateral oophorectomy. Male subjects must use a condom and spermicide if their partner has had a tubal ligation. During the trial, male subjects must not have sex with a woman who is pregnant or breastfeeding, without using a condom.

4. Women of childbearing potential must have a negative pregnancy test (at screening and at each admission), be nonlactating, be using a highly-effective form of birth control for 1 month before enrollment (confirmed by the Investigator), and be willing to use a highly-effective form of birth control during the study and until 3 months after their last dose of IP. Women of nonchildbearing potential must fulfill 1 of the following criteria:

   - Postmenopausal, defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle stimulating hormone (FSH) levels in the laboratory-defined postmenopausal range

   - Have documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy (but excluding tubal occlusion) at least 12 months prior to screening

5. Have a body mass index (BMI) between 18 and 30 kg/m^2 and weigh at least 50 kg and no more than 100 kg

4.2 Exclusion criteria

Subjects must not be randomised in 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 renal disease or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs

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

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

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

6. Any clinically significant abnormalities in the physical examination, 12-lead ECG, or vital signs, as judged by the Investigator

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

8. Current smokers, those who have smoked or used nicotine products within the previous 3 months

9. History of alcohol abuse or excessive intake of alcohol as judged by the Investigator

10. Positive screen for drugs of abuse screening or smokerlyzer test at or on admission to the study centre or positive screen for alcohol breath test on admission to the study centre prior to the first administration of the investigational product

11. 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

12. 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)

13. Use of any prescribed or non-prescribed medication including antacids, analgesics other than paracetamol/acetaminophen, herbal remedies, vitamins, and minerals during the 2 weeks prior to the first administration of the investigational product 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 female subjects is allowed

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

15. 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 administration of

investigational product in this study. The period of exclusion begins at the time of the last visit of the previous study. Note: subjects consented and screened, but not dosed in this study or a previous Phase I study, are not excluded

16. Creatinine clearance <80 mL/min based on the Cockcroft-Gault Formula:

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

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

where age is expressed in years, weight in kg, and serum creatinine (S_{Cr}) in mg/dL

17. Previous randomisation to treatment 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 subject 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 study data or are considered unlikely to comply with study procedures, restrictions and requirements

For procedures for handling incorrectly randomised subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

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

1. Fast for at least 4 hours prior to the clinical laboratory evaluation at screening and during the residential period

2. Eat and drink only the standardised meals and drinks provided (apart from water) during the residential period in the study centre

3. Abstain from consuming any of the following:

   - Alcohol from 72 hours before admission, 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 admission, 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 consent until after the follow-up visit

4. Abstain from nicotine use, smoking, and drugs of abuse from time of consent until after follow-up

5. Abstain from taking any medication (prescribed or over the counter products), other than paracetamol/acetaminophen, and hormone replacement therapy, from 2 weeks prior to the first administration of the investigational product until after the follow-up visit. However, this should not obviate necessary medical treatment. If any medication is necessary during the residential period, it should be prescribed by the Investigator and the AstraZeneca Clinical Pharmacology Alliance (CPA) Physician should be informed (Section 5.6).

6. Subjects should refrain from strenuous physical activity, which is not within the subject's normal daily routine, from 7 days prior to admission to the study centre until after the follow-up visit

7. Abstain from blood or plasma donation until 3 months after the follow-up visit

8. Male subjects should use a condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm or fathering a child from the first administration of the investigational product until 3 months after the last administration of the investigational product. Female partners of male volunteers must use another form of highly effective contraception from the time the male volunteer receives the first dose until 3 months after the last dose

9. Women of childbearing potential must be using a highly-effective form of birth control for 1 month before enrollment (confirmed by the Investigator), and be willing to use a highly-effective form of birth control during the study and until 3 months after their last dose of IP.

5.2 Subject enrolment and randomisation

The Investigator will ensure that:

1. Signed informed consent is obtained from each potential subject before any study-specific procedures are performed

2. Each potential subject is assigned a unique enrolment number, beginning with "E#"

3. The eligibility of each subject is determined (see Sections 4.1 and 4.2)

4. Each eligible subject is assigned a unique randomisation code (subject number), beginning with "#"

Randomisation will be performed on the morning of the first dose.

Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation.

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

5.2.1 Procedures for randomisation

A randomisation scheme will be produced by using the AstraZeneca global randomisation system (GRand). Subjects will be allocated to ceftaroline fosamil or placebo (15 subjects to ceftaroline fosamil and 5 subjects to placebo per cohort). The randomisation will be done for each cohort using consecutive randomisation codes (subject numbers).

5.3 Procedures for handling incorrectly randomised subjects

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

Where a subject, who does not meet the inclusion and/or exclusion criteria, is randomised in error and this is identified before the investigational product administration, the subject should be withdrawn from the study. A discussion should occur between the AstraZeneca CPA Physician and the Investigator regarding whether a replacement may be considered.

Where a subject, who does not meet the selection criteria, is randomised in error and started on treatment, or where a subject subsequently fails to meet the study criteria post-initiation, the Investigator should inform the AstraZeneca CPA Physician immediately. Although treatment should be discontinued, the subject should be advised to continue assessments to ensure their safety.

The AstraZeneca CPA Physician is to ensure all decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

This study is double-blind with regard to treatment (ceftaroline fosamil or placebo) at each dose level. The following staff will have access to the randomisation list:

- The AstraZeneca staff carrying out the labelling and packaging of the investigational product
- The pharmacy staff preparing the investigational product at the study centre

- The staff analysing the PK samples

The randomisation list should be kept in a secure location until the end of the study.

As the IP has a yellow tinge and there is blinding risk, the iv bags will be covered and tubing will be amber (see handling instructions) to maintain the blind..

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the investigators or pharmacists at the study centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Table 2 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Ceftaroline fosamil	30 mg/mL intravenous infusion (600 mg)	
Placebo	0.9% sodium chloride	AstraZeneca

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.

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 iv solutions should be administered promptly, however the drug 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.

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 pharmacists regarding dose preparation and administration.

5.5.2 Doses and treatment regimens

Each subject will receive a single infusion of ceftaroline fosamil or placebo on the morning of Day 1 and Day 8.

Repeated infusions will start on Day 2 and continue through Day 7. Ceftaroline fosamil (600 mg) or placebo will be administered every 12 hours over 1 hour to subjects in Cohort 1 (total daily dose 1200 mg) and every 8 hours over 2 hours to subjects in Cohort 2 (total daily dose 1800 mg).

On Days 1 and 8, subjects will be required to empty their bladders 15 minutes prior to the start of the PK urine sample collections and will be asked to drink 240 mL of water after bladder emptying.

After the investigational product administration, subjects will remain on their beds or sitting for as long as necessary for the required study procedures.

Subjects will fast from 1 hour before to 1 hour after the end of the infusion.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling.

5.5.4 Storage

The investigational product should be kept in a secure place under appropriate storage conditions (see Section 5.5.1). The investigational product label specifies the appropriate storage conditions.

5.6 Concomitant and post-study treatment(s)

Apart from paracetamol/acetaminophen and hormone replacement therapy, no concomitant medication or therapy will be allowed. The subjects should be instructed that no other

medication is allowed including herbal remedies, vitamin supplements, and over-the-counter products without the consent of the Investigator.

Medication, which is considered necessary for the subject'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). When any medication is required, it should be prescribed by the Investigator who should inform the AstraZeneca CPA Physician. Following consultation with the CPA Physician, the Investigator should determine whether or not the subject should continue in the study.

5.7 Treatment compliance

The administration of all medication (including the investigational product) 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, dates, and times of administration of the investigational product will be recorded and checked by the monitor at monitoring visits.

5.7.1 Accountability

It is the Investigator's responsibility to establish a system for handling study treatments, including the investigational product, to ensure that:

1. Deliveries of such products from AstraZeneca are correctly received by a responsible person (eg, Pharmacist)

2. Such deliveries are recorded

3. The investigational product is handled and stored safely and properly

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

5. The study staff will account for all investigational products received at the study centre, administered to the subjects, and returned to the pharmacy. Any discrepancies should be documented, investigated, and appropriately resolved

6. At the end of the study, the study centre staff will account for all unused drugs and for appropriate destruction. Certificates of delivery and destruction should be signed

5.8 Discontinuation of investigational product and withdrawal from study

Subjects may be discontinued from investigational product in the following situations:

- Subject decision. The subject is at any time free to withdraw his/her participation in the study, without prejudice
- AEs
- Severe non-compliance to the CSP, as judged by the Investigator and/or AstraZeneca
- Randomisation in error (see Section 5.3)

Investigational product administration for any individual subject will be stopped if the subject experiences a possible drug-related SAE or a possible drug-related significant non-serious AE, which in the opinion of the Investigator or Sponsor, warrants discontinuation from the study for that subject's well-being.

Subjects who discontinue investigational product administration will be withdrawn from the study.

Subjects who are withdrawn from the study by the Investigator due to AEs after the start of the investigational product administration will not be replaced. Subjects who withdraw for any reason before the first investigational product administration or for reasons other than AEs after the start of the investigational product administration may be replaced.

5.8.1 Study stopping criteria

Investigational product administration in this study will be stopped if an SAE with a reasonable possibility of a causal relationship to the investigational product is reported for 2 or more subjects.

5.8.2 Procedures for withdrawal of a subject from the study

Subjects are at any time free to withdraw from the study (study treatment and assessments), without prejudice (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, subjects who withdraw from the study after the start of investigational product administration and before completion should be seen by an Investigator and undergo the assessments and procedures scheduled for the follow-up visit. Adverse events should be followed up (see Sections 6.3.4 and 6.3.5).

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of these assessments are detailed in the study plan (see Figure 2 and Figure 3).

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

1. ECG

2. Blood pressure and pulse rate

3. PK blood sample (to be taken at the scheduled time point)

4. Safety and laboratory assessments

6.1 Recording of data

The investigator will ensure that data are recorded on the CRF as specified in the CSP. He/she ensures the accuracy, completeness, and timeliness of the data recorded, for data queries and all required reports according to any instructions provided.

The Principal Investigator or study physician will sign the completed CRFs. A copy of the completed CRFs will be archived at the study centre.

6.2 Enrolment and screening procedures

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

Demographic data and other characteristics will be recorded and will include date of birth, gender, and race.

The eligibility of subjects will be determined during a screening period of up to 28 days. This will consist of the following and can be performed over more than 1 day:

1. A standard medical, medication and surgical history with review of the inclusion and exclusion criteria with the subject

2. A complete physical examination

3. Height, weight, and calculation of BMI

4. Vital signs – resting supine blood pressure and pulse rate

5. Recording a resting 12-lead paper ECG

6. A blood sample for routine clinical chemistry, haematology, LH and FSH (female subjects), and screen for the hepatitis B surface antigen, antibodies to the hepatitis C virus, and antibodies to HIV

7. A urine sample for routine urinalysis, alcohol breath test and drugs of abuse screen, smokerlyzer test and pregnancy test (female subjects)

8. Creatinine clearance estimation

9. Recording of concomitant medication use and SAEs

After admission to the study centre and before randomisation the Investigator should reassess each subject to reconfirm eligibility.

6.2.1 Follow-up procedures

A post-study medical examination will be performed 7 to 10 days after discharge from the study centre on Day 9. This will be similar to the examination performed at screening and will include a brief physical examination, measurement of weight, vital signs, recording a 12-lead paper ECG, a blood sample for clinical chemistry, haematology, a urine sample for urinalysis and pregnancy test (female subjects), and assessment of any AEs or required medication. In addition additional follow-up will be performed where:

- a subject has an unresolved adverse event at the follow-up visit, which, in the opinion of the investigator, merits further follow-up;

- new information becomes available that supports an extended follow-up period.

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 Local tolerability measurements

Local tolerability will be assessed over time and graded using the VIP in Appendix E. These assessments will occur as specified in Figure 2. The VIP score will be recorded for all local reactions; any local reactions with a VIP score of 2 or greater will be determined an ISR and will be recorded as an AE.

The Investigator, or delegate, will assess the onset of ISR (eg, inflammation) by examining the catheter insertion site under good lighting conditions for the presence of erythema, tenderness, induration, swelling, drainage, or presence of palpable cord. Each infusion site will be assessed and either found to be unremarkable, ie, no evidence of ISR or presence of an ISR. When an ISR occurs the following information will be recorded on a separate source document: date and time, detailed description (including location, infusion volume, presence or absence of a palpable venous cord, and the extent [length and width] of inflamed tissue), and severity findings. The Investigator will record, report, and monitor the ISR as an AE when the severity score is 2 or more as measured by the VIP scale included in Appendix E.

6.3.2 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 wash-out periods, even if no investigational product has been administered.

The term AE is used generally to include any AE whether serious or non-serious.

6.3.3 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, wash-out, 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 one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B of this CSP. For the definition of other significant adverse events (OAEs) see Section 10.1.1.

6.3.4 Recording of adverse events

Time period for collection of adverse events

Serious adverse events will be collected from provision of informed consent and AEs will be collected from randomisation throughout the treatment period and including the follow-up period.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit 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 collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome

Additional variables will be collected for all SAEs including treatment given for the event.

The following intensity ratings will be used:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)
3. Severe (incapacitating, with inability to perform normal activities)

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 6.3.3. 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 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, the 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 of this 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 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 laboratory tests, vital signs, ECGs, and other safety assessments will be summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs, and other 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 laboratory value or vital signs measurement is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital signs measurement 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 the 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.

6.3.5 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 Investigators or other study centre staff will inform the appropriate AstraZeneca representatives within 24 hours of when he/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 will inform the 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/she becomes aware of it.

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

6.3.6 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the study plan (see Figure 2). The date and time of collection of all laboratory tests will be recorded in the appropriate CRF.

The safety laboratory variables are presented in Table 3.

Table 3 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**
HIV and Hepatitis B and C[a]	Follicle-stimulating hormone (female subjects only)[a]
	Luitenising hormone (female subjects only)
Pregnancy test in female subjects only (beta HCG)[a]	Creatinine clearance

a At screening only.

HIV: human immunodeficiency virus.

Subjects will fast for 4 hours before laboratory measurements at screening and during the residential period. Fasting is not required for follow-up measurements.

Luitenising hormone and FSH will be measured in female subjects to determine menopausal status.

Urine will be tested for the following drugs of abuse at screening and admission: amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, morphine, tetrahydrocannabinol, and opiates. Smokerlyzer test will be performed. Subjects will be screened for alcohol at screening and admission (alcohol breath test). A serum pregnancy test will be conducted at screening and urine pregnancy tests will be performed at admission, and follow-up. If a subject tests positive to any of these screening tests he/she will be excluded from the study.

A urine sample for urinalysis and microscopy is to be collected along with the other clinical laboratory evaluations. Microscopy will be performed as per HMR procedures.

Creatinine clearance will be estimated using the Cockroft-Gault formula at screening 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 S_{Cr} in mg/dL.

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated (eg, ALT >2 x ULN, 80 U/L [whichever is the lowest], 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 or if already randomised will be followed until normalisation or for 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.

The samples for clinical chemistry, haematology, and urinalysis will be analysed using routine methods at the HMR Laboratory in the United Kingdom.

For blood volume see Section 7.1.

6.3.7 Physical examination

The timing of individual examinations is indicated in the study plan (Figure 2).

A complete physical examination will be performed at screening and at admission and discharge from the study centre and include an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculo-skeletal, cardiovascular, respiratory, and neurological systems. On Day 5 and at the follow-up visit, only a brief physical examination is required.

Brief physical examination includes: general appearance, skin, head and neck, lymph nodes, cardiovascular status, respiratory and abdomen.

Height will be measured in centimetres and weight in kilograms. Measurements should be taken without shoes and the same scale used for all measurements. Subjects' BMI will be calculated from the height and weight.

Height and weight will be evaluated at screening, but only weight will be evaluated at the follow-up visit.

6.3.8 ECG

For timing of assessments refer to the study plan (Figure 2).

The 12-lead paper ECGs will be obtained after 10 minutes supine rest at pre-dose and during study days. Only the overall evaluation (normal/abnormal) will be recorded in the CRF.

6.3.9 Vital signs

6.3.9.1 Pulse and blood pressure

For timings of assessments refer to the study plan (Figure 2).

Supine blood pressure and pulse will be measured after at least 10 minutes supine rest on a bed. If possible, the same equipment should be used for each evaluation. It is preferable to avoid the arm with a cannula.

6.4 Pharmacokinetics

For investigational product administrations, 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 pharmacokinetic samples

Venous blood samples (approximately 4 mL per sample) for the determination of ceftaroline fosamil (the prodrug of ceftaroline), ceftaroline, and ceftaroline M-1 (the metabolite of ceftaroline) concentrations in plasma will be taken at the time points presented in Figure 3.

Urine samples for determination of concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 in urine will be taken from the total urine sample provided during each collection period presented in Figure 3. Subjects will be required to empty their bladders prior to the start of the urine sample collection and will be asked to drink 240 mL of water after bladder emptying. The weight and the derived volume of the urine collected over each urine collection interval will be calculated.

The date and time of collection of each blood sample will be recorded. The start and stop date and time of collection of each pooled urine sample will also be recorded.

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

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 concentration in plasma and urine will be analysed by on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method 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 time of receipt by the bioanalytical laboratory will be analysed.

For each placebo subject, samples will only be analysed on a 'for cause' basis, eg, if no quantifiable concentrations were observed in a subject's samples when the drug was expected to be present.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites. Any results from such analyses may be reported separately from the clinical study report.

Additional analyses will be conducted on the biological samples to investigate the reproducibility of the analytical results in incurred samples. Any results from such analyses will only be used to confirm the reproducibility of the method and will be reported in a separate table in the bioanalytical study contribution report.

6.5 Biomarkers

6.5.1 Collection of exploratory biomarker sample

A total of 40 mL blood will be collected at each of the time points presented in the study plan (Figure 2) for potential future exploratory research aimed at exploring biomarkers involved in the PK, PD, safety, tolerability, and efficacy of ceftaroline fosamil.

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

For blood volume see Table 4.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject is presented in Table 4.

Table 4 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)[a]	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.5	5	12.5
	Haematology	2	5	10
	Serology	2.5	1	2.5
Follicle-stimulating hormone and serum pregnancy test[b]		2.5	1	2.5
Pharmacokinetics				
Cohort 1 (600 mg 1-hour infusion q12h)		4	44	176
Cohort 2 (600 mg 2-hour infusion q8h)		4	43	172
Exploratory biomarker		40	2	80
Total				**283.5 / 279.5**

[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] Female subjects only.

The number of samples taken, 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 in this section.

7.2.1 Safety samples

Safety samples will be disposed of after analysis.

7.2.2 Pharmacokinetic samples

Samples will be disposed of after the CSR has been finalised, unless retained for future analyses.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate 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 clinical study report. Any results from such analyses will be reported separately from the clinical study report

7.2.3 Exploratory biomarker samples

Biological samples for biomarker research can be retained on behalf of AstraZeneca for a maximum of 15 years following the last subject's last visit in the study. The results from future analysis will not be reported in the CSR, but separately in a Scientific Report.

7.3 Labelling and shipment of biohazard samples

The Investigator ensures 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 is maintained for all samples throughout their life cycle.

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

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

AstraZeneca oversees the entire life cycle 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 life cycle of the sample.

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, if not already analysed and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

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

The Investigator will:

- Ensure that the subject's withdrawal of informed consent for 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 or destroyed, and the action documented
- Ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or 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 ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or 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 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 staff.

The opinion of the EC should be provided 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 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, the EC, and the Investigator with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

8.4 Informed consent

Any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation should be described in the informed consent form that is approved by an EC.

The Investigator will:

- Ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure that each subject is notified that they are free to withdraw 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(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form(s) is/are given to the subject.

8.5 Changes to the protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the 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 Protocol).

The Amendment should be approved by the EC and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised Protocols.

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 Informed Consent Form, AstraZeneca and the EC should 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

will manage the 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 stud centre to:

- Determine the adequacy of the facilities
- Determine availability of subjects appropriate 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 staff

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 staff and also train them in any study-specific procedures and system(s) utilised.

The Investigator will ensure that 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 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 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 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 CSP shall prevail with respect to the

conduct of the study and the treatment of subjects and in all other respects, 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 follows 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 Q2 2012 and to end by Q4 2012.

The study may be terminated 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.

When the completed paper CRFs have been scanned and indexed, the data are entered into the study database and proofread.

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 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, signed and locked, clean file will be declared.

Evaluation and calculation of variables

10.1 Calculation or derivation of safety variable(s)

10.1.1 Other significant adverse events

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 AEs leading to premature discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the CPA Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory, vital signs, and ECG 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.

10.2 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma and urine concentration data for ceftaroline fosamil (the prodrug of ceftaroline), ceftaroline, and ceftaroline M-1 (the metabolite of ceftaroline) will be performed at 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. In addition, for the purpose of calculating time deviations and graphical presentations of the concentration versus time profiles, the nominal time will be converted to unit of hour for PK protocol time points that are in unit of minute.

Pharmacokinetic parameters will be derived using non-compartmental 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). Graphics may be prepared with SAS® Version 9.2, or higher; or SigmaPlot® 9.0, or higher (Systat Software Inc., San Jose, California, 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 study report. In brief, the estimation steps are as follows:

1. Analyse the concentration-time data using an intravenous (IV) 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 IV 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 listed separately in the study report. Imputations for the end-of-infusion concentrations will not be performed for ceftaroline and ceftaroline M-1.

Where possible, the following plasma and urine PK parameters will be determined for ceftaroline fosamil (the prodrug of ceftaroline), ceftaroline, and ceftaroline M-1, unless otherwise noted. Other PK 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.

Following the single-dose part in both cohorts of the study:

The following plasma PK parameters of all 3 analytes on Day 1 will be calculated:

- 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 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] (to be calculated for Cohort 1 only)
- Area under the plasma concentration-time curve from zero to 8 hours after the start of the infusion [$AUC_{(0-8)}$, µg·h/mL] (to be calculated for Cohort 2 only)
- Apparent terminal rate constant (λ_z, 1/h)
- Terminal half-life ($t_{1/2\lambda z}$, h), determined as $\ln(2)/\lambda_z$
- Metabolite/parent C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,Cmax}$) (adjusted for differences in molecular weights)
- Metabolite/parent AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,AUC}$) (adjusted for differences in molecular weights)

In addition, the following plasma PK parameters will be calculated for ceftaroline and ceftaroline fosamil:

- 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 urine PK parameters on Day 1 will be calculated for all 3 analytes:

- Amount of analyte excreted in the urine (A_e, mg). The amount will be calculated for each interval and cumulatively
- Fraction of dose excreted into urine ($f_{e,}$%) calculated as A_e divided by dose, for each interval and cumulatively
- Total fraction of dose excreted in urine ($f_{e,total}$,%) calculated as (ceftaroline fosamil f_e+ceftaroline f_e+M-1 f_e), for each interval and cumulatively
- Renal clearance (CL_R, L/h), calculated as cumulative A_e over 24 hoursdivided by $AUC_{(0-t)}$ over 24 hours

Following the multiple-dose part in both cohorts of the study:

The following plasma PK parameters of all 3 analytes will be calculated for Day 4 and Day 8:

- Maximum plasma concentration at steady state during dosing interval ($C_{ss,max}$, µg/mL)
- Time to maximum concentration at steady state during dosing interval ($t_{ss,max}$, h), obtained directly from the observed concentration versus time data
- Minimum plasma concentration at steady state during dosing interval ($C_{ss,min}$, µg/mL)
- Area under the plasma concentration-time curve from zero to time of the last quantifiable concentration [$AUC_{(0-t)}$, µg·h/mL]

- Area under the plasma concentration-time curve from zero to the end of the dosing interval (AUC_{τ}, µg·h/mL), where τ is 12 hours for Cohort 1 and 8 hours for Cohort 2
- Average plasma concentration during the dosing interval ($C_{ss,av}$, µg/mL)
- Fluctuation index (FI, %) calculated as $[(C_{ss,max}-C_{ss,min}) / C_{ss,av}] * 100$
- Metabolite/parent C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,Cmax}$) (adjusted for differences in molecular weights)
- Metabolite/parent AUC_{τ} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,AUC}$) (adjusted for differences in molecular weights)
- Apparent terminal rate constant (λ_z, 1/h)
- Terminal half-life ($t_{½\lambda z}$, h), determined as $\ln(2)/\lambda_z$
- Accumulation ratio based on C_{max} [$R_{ac(Cmax)}$] calculated as $C_{max,Day\ 4}/C_{max,Day\ 1}$ and $C_{max,Day\ 8}/C_{max,Day\ 1}$
- Accumulation ratio based on AUC [$R_{ac(AUC)}$] calculated as $AUC_{\tau,Day\ 4}/AUC_{(0\text{-}12),Day\ 1}$ and $AUC_{\tau,Day\ 8}/AUC_{(0\text{-}12),Day\ 1}$ for Cohort 1; as $AUC_{\tau,Day\ 4}/AUC_{(0\text{-}8),Day\ 1}$ and $AUC_{\tau,Day\ 8}/AUC_{(0\text{-}8),Day\ 1}$ for Cohort 2
- Linearity factors calculated as $AUC_{\tau,Day\ 4}/AUC_{Day\ 1}$ and $AUC_{\tau,Day\ 8}/AUC_{Day\ 1}$

In addition, the following plasma PK parameters of ceftaroline and ceftaroline fosamil will be calculated for Day 4 and Day 8:

- Mean residence time (MRT, h)
- Plasma clearance at steady state (CL_{ss} for ceftaroline fosamil, apparent CL_{ss} 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 urine PK parameters will be calculated for Day 8:

- Amount of analyte excreted in the urine ($A_{e,ss}$, mg); the amount will be calculated for each interval and cumulatively up to the end of the dosing interval (12 hours for Cohort 1 and 8 hours for Cohort 2)

- Fraction of dose excreted into urine ($f_{e,ss,}$%) calculated as $A_{e,ss}$ divided by dose for each interval and cumulatively up to the end of the dosing interval (12 hours for Cohort 1 and 8 hours for Cohort 2)

- Total fraction of dose excreted in urine ($f_{e,ss,total}$,%) calculated as (ceftaroline fosamil $f_{e,ss}$+ceftaroline $f_{e\ ,ss}$+M-1 $f_{e\ ,ss}$) for each interval and cumulatively

- Renal clearance ($CL_{R,ss}$, L/h), calculated as cumulative $A_{e,ss}$ divided by AUC_{τ} over 12 hours for Cohort 1; and cumulative $A_{e,ss}$ divided by AUC_{τ} over 8 hours for Cohort 2

The following PK parameters from both the single- and multiple-dose parts of the study will be calculated for diagnostic purposes and listed but not summarised:

- 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.

- Goodness of fit statistic 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.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 General principles

The analysis of data will be based on different subsets according to the purpose of analysis, ie, for safety and PK, respectively. The decision regarding validity of data for each of the analysis sets will be based on a blind review of data.

The as-treated principle will be applied to all evaluations; ie, subjects who received a treatment other than the one assigned in the randomisation list will be analysed as belonging to the actual treatment group and not that assigned by randomisation.

11.1.2 Safety analysis set

All subjects who received at least one dose of randomised investigational product, and for whom any post-dose data are available will be included in the safety analysis set.

11.1.3 PK 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 urine 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.

11.2 Methods of statistical analyses

11.2.1 General principles

Data will be presented by actual dose (not by cohort), and subjects receiving placebo will be pooled across dosing cohorts for the purposes of summarising the safety results.

Given the exploratory nature, no formal statistical hypothesis testing will be performed in this study. Since no planned formal testing will be performed in this study, and the confidence intervals that will be calculated are only for descriptive purposes, no corrections for multiplicity will be used.

Missing data will result in a reduced sample size for that parameter. Since the statistical analyses will be predominantly presentations in tables and individual data listings, no action will be taken to handle missing data.

A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

11.2.2 Subject characteristics

Continuous variables will be summarised using descriptive statistics (n, mean, standard deviation [SD], minimum [min], median, maximum [max]) by treatment group. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment group.

11.2.3 Safety and tolerability

Continuous variables will be summarised using descriptive statistics (n, mean, SD, min, median, max) by treatment group. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment group. Graphical presentations will be used as

appropriate. Examples may include line graphs showing individual or mean development over time, and shift plots showing pre-treatment values on horizontal axis and post-treatment values on vertical axis.

All AEs will be collected for each subject from the time when informed consent is obtained (Visit 1) until the follow-up visit. AEs that occur before dosing will be reported separately.

Adverse events will be summarised by Preferred Term (PT) and System Organ Class (SOC) using MedDRA. 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.

11.2.4 Pharmacokinetics

Individual PK blood and urine sample collection times, as well as derived sampling time deviations, and concentration-time data will be listed. Individual plasma concentration-time profiles of the 3 analytes will be depicted on linear and semi-logarithmic scales.

Pharmacokinetic data will be presented by analyte, cohort, and study day as appropriate.

Plasma concentrations will be summarised by nominal time points using descriptive statistics including: the population size (N for sample size and n for available data), geometric mean, geometric coefficient of variation (CV%), arithmetic mean, SD, median, min, and max.

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.

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 below the LLOQ (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 max value will be reported from the individual data, and the min 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, min, median, and max
- The number of BLQ values (n below LLOQ) will be reported for each time point

Plasma and urine PK parameters will be summarised by analyte, cohort, and/or study day as appropriate using descriptive statistics including: N, n, geometric mean, CV%, arithmetic mean, SD, median, min, and max.

Visual assessments of steady state

Mean (±SD) and individual predose/trough concentration-time profiles of each analyte during the multiple-dose period will be presented by dose group for visual assessments of steady state.

11.3 Determination of sample size

Due to the exploratory nature of the study the sample size is not based on formal statistical considerations. The sample size is based on experience from previous similar Phase I studies with other compounds.

12. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

12.1 Medical emergencies and AstraZeneca contacts

The 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 6.3.5.**

In the case of a medical emergency the Investigator may contact the CPA Physician. If the CPA Physician is not available, contact the CPA Programme Director at AstraZeneca.

Name	Role in the study	Address & telephone number

12.2 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 during the course of the study, then the Investigator or other study centre staff will inform the appropriate AstraZeneca representatives **within 1 day**, ie, immediately but no later than **the end of the next business day** of when he/she becomes aware of it.

The designated AstraZeneca representative works 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 given. Ceftaroline can be removed by haemodialysis. In subjects with end stage renal disease administered 400 mg of ceftaroline fosamil, the mean total recovery of ceftaroline in the dialysate following a 4-hour haemodialysis session started 4 hours after dosing was 76.5 mg (21.6% of the dose). However, no information is available on the use of haemodialysis to treat an overdose.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.3.5. For other overdoses, reporting should be done within 30 days.

12.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be reported to AstraZeneca using the appropriate forms.

12.3.1 Maternal exposure

Should a pregnancy occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

12.3.2 Paternal exposure

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

Pregnancy of a 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 monitored and documented from the first administration until 3 months after the last administration of the investigational product.

13. LIST OF REFERENCES (NOT APPLICABLE)

Clinical Study Protocol Appendix A

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00010
Edition Number	1

Appendix A
Signatures

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 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 jeopardize 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 iv 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
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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

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

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

- Review each laboratory report and if a subject has an increase in AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit:
  - Notify the AstraZeneca representative
  - Promptly enter the laboratory date into the laboratory CRF.

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- 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.

1.2.2 Potential Hy's Law Criteria met

If the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the AZ representative who will then inform the central 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 Liver CRF Modules.

- 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.

1.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician 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 Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP,

For the purpose of this process a Hy's Law case is defined as:

Any subject with an increase in both Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum Alkaline Phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug

If there **is** an agreed alternative explanation for the AST or ALT **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** other explanation that would explain the AST or ALT and TBL elevations:

- 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

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm

Clinical Study Protocol Appendix E

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00010
Edition Number	1

Appendix E
Infusion Site Reaction Assessment

1. INFUSION SITE REACTION ASSESSMENT

An infusion site reaction (ISR) is defined as an adverse event (AE) or laboratory abnormality possibly related to the peripheral cannula (eg, insertion, patency, maintenance) or the actual infusion of the study drug or placebo, judged by the Investigator or AstraZeneca. An ISR may commence at any time during the intravenous infusion administration. The most common examples of ISR that may be related to study drug and or vehicle include:

- Infiltration: The escape of nonvesicant solutions into the extravascular tissue causing local swelling and possible irritation
- Phlebitis: Inflammation of the vein and the surrounding tissue, caused by mechanical and/or chemical (study drug/vehicle) injury
- Thrombophlebitis: Inflammation of the vein and surrounding tissue caused by intravascular clot formation

Other nondrug-related cases of ISR should also be considered. **The clinical staff will assess the infusion site as described in CSP Section 6.3.1**. The Investigator will assess the onset of ISR (eg, inflammation) by examining the catheter insertion site under good lighting conditions for the presence of erythema, tenderness, induration, swelling, drainage, or presence of palpable cord. The Investigator will record and monitor the ISR as an AE and denote in the subject's clinic notes ISR, date and time, pertinent vitals, detailed description (including presence or absence of a palpable venous cord and the extent [length and width] of inflamed tissue), physical examination, laboratory (if indicated), severity findings, assessment, and plan. For all ISR AEs, severity should be assessed and reported utilizing the Visual Infusion Phlebitis (VIP) scale appended below.

Subsequent clinic notes should report progression (eg, scale score, if indicated) and date of resolution. Based on the Investigator's medical judgment, subjects experiencing an ISR related to inflammation at the catheter site should have the following considered:

- A digital photograph taken of the involved site (including a ruler in the field of view to allow the quantitation of the extent of inflammation)
- Peripheral Doppler Study: If thrombophlebitis is suspected
- Change of infusion insertion site (see below)

2. MODIFIED VISUAL INFUSION PHLEBITIS SCALE

IV Site Appears Healthy	0	No signs of phlebitis OBSERVE CANNULA
One of the following is evident: • Slight pain near IV site OR • Slight redness near IV site	1	Possibly first signs of phlebitis OBSERVE CANNULA
Two of the following are evident: • Pain at IV site • Erythema • Swelling	2	Early stage of phlebitis **Record as Adverse Event**: Infusion Site Phlebitis **Action**: Discontinue further infusion/s and remove cannula in affected arm
ALL of the following signs are evident and extensive: • Pain along path of cannula • Erythema • Induration	3	Medium stage of phlebitis **Record as Adverse Event**: Infusion Site Phlebitis **Action**: Discontinue further infusion/s and remove cannula in affected arm. Consider treatment
ALL of the following signs are evident and extensive: • Pain along path of cannula • Erythema • Induration • Palpable venous cord	4	Advanced stage of phlebitis or the start of thrombophlebitis **Record as Adverse Event**: Infusion Site Phlebitis **Action**: Discontinue further infusion/s and remove cannula in affected arm. Consider treatment
ALL of the following signs are evident and extensive: • Pain along path of cannula • Erythema • Induration • Palpable venous cord • Pyrexia	5	Advanced stage of thrombophlebitis **Record as Adverse Event**: Infusion Site Thrombophlebitis **Action**: Discontinue further infusion/s and remove cannula in affected arm. Initiate treatment

IV intravenous.

Phlebitis scale, Jackson 1998. With permission from "Andrew Jackson, IV Nurse Consultant. The Rotherham NHS Foundation Trust, UK"