Clinical Study Protocol

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00015 (P903-30)
Edition Number	1
Date	

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

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

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

Principal Investigator

Study center(s) and number of subjects planned

This study will be conducted in 2 parts at a single center in the United Kingdom.

Initially, approximately 32 healthy male and female volunteers will be enrolled in Part A to ensure a total of 24 evaluable volunteers (50 mL infusion volume). An additional 32 volunteers may be enrolled to assess a 100-mL infusion volume following review of the 50 mL data. For Part B, 10 healthy male and female volunteers will be enrolled to ensure completion of at least 8 volunteers.

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

Objectives

Primary objective

The primary objective of Part A is to evaluate the local tolerability of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions).

The primary objective of Part B is to characterize the pharmacokinetics of ceftaroline in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes.

Secondary objectives

The secondary objective of Part A is to evaluate the safety of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions).

The secondary objectives of Part B are:

- To characterize the pharmacokinetics of ceftaroline fosamil (the prodrug of ceftaroline) and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes

- To evaluate the safety and tolerability of ceftaroline in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes

Study design

This is a Phase I, single-center, 2-part, randomized study to assess the local tolerability, safety, and pharmacokinetics of ceftaroline in healthy male and female adult volunteers, aged 18 to 75 years, inclusive. Part A will utilitze a placebo-controlled, double-blind, multiple-dose, 2-way crossover design to assess the local tolerability of ceftaroline following multiple infusions of ceftaroline fosamil 600 mg and placebo, each in 50-mL and 250-mL infusion volumes. If the subjects receiving the active 50-mL infusion volume have an incidence of infusion site reactions of >40%, Part A may be repeated using 100-mL and 250-mL infusion volumes. The decision will be made following discussion between the Investigator and the Sponsor and will be based on review of the 50 mL, 250 mL (and corresponding placebo) data. Part B will be conducted following Part A and will utilize an open-label, single-dose, 2-way crossover design to evaluate the pharmacokinetics of ceftaroline in either 50-mL and 250-mL infusion volumes or 100-mL and 250-mL infusion volumes, depending on the safety and local tolerability results from Part A.

Part A (Assessment of local tolerability)

Part A of the study is a randomized, placebo-controlled, double-blinded, and 2-way crossover design. Infusion volumes of 50 mL and 250 mL will be studied to facilitate the identification of effects related to the administration of drug diluted in various infusion volumes rather than the study procedures or situations. Initially, 32 volunteers will be enrolled to ensure a total of 24 evaluable volunteers. An additional 32 volunteers may be recruited and dosed to compare a 100 mL infusion volume against the 250-mL infusion volume.

Investigational product will be administered as simultaneous, bilateral (placebo in one arm and active in the other), 60-minute infusions every 12 hours over 72 hours (6 infusions) followed by a minimum 4.5-day (approximately 108 hours) washout and another simultaneous, bilateral, 60-minute infusion (in different veins than used previously) every

12 hours over 72 hours (6 infusions). The following treatments will be administered in Part A:

- Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume
- Treatment B: placebo in 50 mL infusion volume
- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume
- Treatment D: placebo in 250 mL infusion volume

On Day 1, volunteers will be randomly assigned in a 1:1 fashion to 1 of 2 treatment sequences of various infusion volumes of ceftaroline fosamil 600 mg and placebo as outlined below:

Sequence	Crossover period	Left arm	Right arm
Sequence 1	1	50 mL active (Treatment A)	250 mL placebo (Treatment D)
	2	50 mL placebo (Treatment B)	250 mL active (Treatment C)
Sequence 2	1	250 mL active (Treatment C)	50 mL placebo (Treatment B)
	2	250 mL placebo (Treatment D)	50 mL active (Treatment A)

These sequences will avoid administering active treatment in the same arm for both treatment periods and will also avoid administering the same volume to both arms within the same treatment period.

If the 50 mL subjects have an incidence of infusion site reactions of >40%, Part A may be repeated, replacing the 50 mL treatments A and B respectively with:

- Treatment E: 600 mg ceftaroline fosamil in 100 mL infusion volume
- Treatment F: placebo in 100 mL infusion volume

The corresponding treatment sequences will be as shown below:

Sequence	Crossover period	Left arm	Right arm
Sequence 3	1	100 mL active (Treatment E)	250 mL placebo (Treatment D)
	2	100 mL placebo (Treatment F)	250 mL active (Treatment C)
Sequence 4	1	250 mL active (Treatment C)	100 mL placebo (Treatment F)
	2	250 mL placebo (Treatment D)	100 mL active (Treatment E)

The study will be comprised of a screening period of up to 28 days, 2 residential periods of approximately 5 days, separated by a washout period of at least 4.5 days (approximately 108 hours), and a follow-up visit 5 to 10 days after discharge from the unit.

Throughout the residential periods, there will be assessment of local tolerability at the infusion site and safety monitoring (including physical examinations, laboratory assessments, 12-lead electrocardiograms, and vital sign measurements). Local tolerability will be assessed over time. Any local reaction with a visual infusion phlebitis score of 2 or greater (see Appendix D) will be determined as an infusion site reaction and will be recorded as an adverse event. Any infusion site reactions unresolved by the follow-up visit will continue to be monitored for as long as the Investigator considers necessary.

Part B (Assessment of pharmacokinetics)

Part B will be conducted following a review of the local tolerability and safety results from Part A. The doses to be used in Part B of the study will be determined following review of the Part A data. If the volunteers receiving the active 600 mg diluted in 50 mL have an ISR ≤40% during Part A, then Part B will include single doses of the following:

- Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume
- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)

Depending on the results from Part A, the alternative single doses of treatment shown below may be administered in Part B:

- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)
- Treatment E: 600 mg ceftaroline fosamil in 100 mL infusion volume

If neither the 50 mL or 100 mL infusion volumes are tolerated then Part B will not be performed.

Volunteers who are randomized in Part A will not be allowed to enroll in Part B. Part B of the study will consist of a screening period of up to 28 days, a 5-day/4-night residential period, and a follow-up period of 5 to 10 days after discharge from the unit. After the screening period, volunteers who qualify will be asked to return for admission to the study center on Day -1 and will remain confined until discharge. On Day 1, volunteers will be randomly assigned in a 1:1 fashion to either treatment sequence CA or AC (or sequence CE or EC if applicable). The arm infused will switch from the first period to the second and thus the randomization will be stratified by the ordering of infusion (Right-Left and Left-Right), to balance any potential arm effects, and to avoid confounding arm with period effects. A single dose of 600 mg ceftaroline fosamil from the appropriate treatment will be administered intravenously over 60 minutes on Day 1. Following a 1-day washout (Day 2), a single dose of 600 mg ceftaroline fosamil from the appropriate treatment will be administered intravenously over 60 minutes on Day 3. Volunteers will be discharged from the unit on Day 4 after

collection of the 24-hour pharmacokinetic sample in Period 2 and completion of all scheduled assessments.

Plasma pharmacokinetic sample collection and safety assessments including physical examinations, laboratory assessments, 12-lead electrocardiograms, and vital sign measurements will be performed.

Target subject population

Healthy male and female volunteers between the ages of 18 to 75 years, inclusive, will be eligible for study participation. Women of childbearing potential must have a negative pregnancy test (at screening and at each admission), be nonlactating, and be using a highly-effective form of birth control for 3 months before enrollment.

Initially, up to 32 volunteers will be enrolled in Part A to ensure a total of 24 evaluable volunteers (50 mL). An additional 32 volunteers may be enrolled to assess the 100-mL infusion volume. Ten volunteers will be enrolled in Part B in order to have 8 evaluable volunteers.

Investigational product, dosage and mode of administration

Ceftaroline fosamil for infusion will be supplied as 600 mg ceftaroline fosamil dry mixture in a clear glass vial. Vials will be reconstituted and diluted in 0.9% sodium chloride infusion fluid to volumes of 50, 100, or 250 mL, as appropriate. For Part A, investigational product will be administered as 60-minute, intravenous infusions every 12 hours for 72 hours (6 infusions) in each of 2 treatment periods. For Part B, a single infusion of 600 mg ceftaroline fosamil over 60 minutes will be administered in each of 2 treatment periods.

Comparator, dosage and mode of administration

Placebo for Part A will consist of 0.9% sodium chloride infusion fluid of various volumes (ie, 50, 100, or 250 mL), as appropriate. Placebo will be administered as simultaneous, 60-minute, intravenous infusions in the opposite arm from the ceftaroline fosamil infusion.

Duration of treatment

For Part A, the duration of each volunteer's participation will be up to approximately 50 days, including a screening period of up to 28 days, two residential periods of approximately 5 days each separated by a washout of at least 4.5 days (≥108 hours between treatments), and a follow-up visit 5 to 10 days following discharge from the final period. The duration of each volunteer's participation in Part B will be up to 43 days including a 28-day screening period, a 5-day residential period, and a follow-up visit 5 to 10 days following clinic discharge.

For both study parts, volunteers will begin the residential stay on Day -1 (of each period in Part A) and will be discharged after completion of all intravenous infusions, all study-related evaluations, and at the discretion of the Investigator.

Outcome variable(s):

- Safety

  adverse events, including local infusion site tolerability, vital signs, electrocardiograms, clinical laboratory variables, and physical examinations

- Pharmacokinetics (Part B only)

  The following plasma parameters will be calculated, where estimable, for ceftaroline, ceftaroline fosamil, and ceftaroline M-1: maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), area under the 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 [$AUC_{(0-12)}$], apparent terminal elimination rate constant (λ_z), half-life associated with the terminal slope ($t_{½\lambda z}$), mean residence time (MRT), total body clearance of drug from plasma (CL, for ceftaroline fosamil and ceftaroline [apparent CL]), volume of distribution based on the terminal phase (V_z, for ceftaroline fosamil and ceftaroline [apparent V_z]), volume of distribution at steady state (V_{ss}, for ceftaroline fosamil and ceftaroline [apparent V_{ss}]), C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,Cmax}$), and AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,AUC}$)

Statistical methods

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. For Part A, a sample size of 24 volunteers is considered sufficient to assess if the low-volume infusion produces an increase in the incidence of infusion site reactions (incidence >40% in subjects on active treatment). Therefore, approximately 32 volunteers will be recruited for Part A for a given treatment comparison (ie, 50 versus 250 mL or 100 versus 250 mL infusion volumes) to ensure the collection of complete data. This sample size is also sufficient to provide adequate safety data in healthy volunteers of the infusion volumes and placebo.

The pharmacokinetic profiles of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 following a single-dose intravenous administration of 600 mg ceftaroline fosamil (diluted in 250 mL) over 60 minutes have been characterized in previous studies. Although the infusion volumes will be different in Part B of the current study, this same dose and infusion duration will be administered across treatments and no major differences in exposures are expected. Data collected from approximately 8 volunteers is deemed adequate to characterize the pharmacokinetics of the 3 analytes in Treatment A (or Treatment E) and Treatment C.

No formal statistical hypothesis testing will be performed in either part of the study. The safety, tolerability, and pharmacokinetic data will be summarized using descriptive statistics, frequency counts, or graphically, as appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol (CSP).

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.2)
AUC	Area under the concentration-time curve from zero to infinity
$AUC_{(0-t)}$	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
$AUC_{ex\%}$	Percent of AUC extrapolated
B	Blood
BCRP	Breast cancer resistance protein
BLQ	Below the lower limit of quantification
BMI	Body mass index
CABP	Community-acquired bacterial pneumonia
CAP	Community acquired pneumonia
CL	Total body clearance of drug from plasma
C_{max}	Maximum plasma concentration
CPA	Clinical Pharmacology Alliance
C_rCL	Creatinine clearance
CRF	Case report form
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
cSSSI	Complicated skin and skin structure infections
cSSTI	Complicated skin and soft tissue infections
CV%	Geometric coefficient of variation
CYP450	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture

Abbreviation or special term	Explanation
ESRD	End-stage renal disease
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
ICH	International Conference on Harmonization
IP	Investigational product
ISR	Infusion site reaction
iv	Intravenous
λ_z	Apparent terminal elimination rate constant
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NA	Not applicable
ND	Not determined
NDA	New Drug Application
OAE	Other Significant Adverse Event (see definition in Section 11.1.2)
OAT	Organic anion transporter
pCRF	Paper case report form
P-gp	P-glycoprotein
PK	Pharmacokinetics
$R_{M/D,Cmax}$	C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline
$R_{M/D,AUC}$	AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline
Rsq	Goodness-of-fit statistic
S	Serum
SAE	Serious adverse event (see definition in Section 6.3.3).

Abbreviation or special term	Explanation
SD	Standard deviation
$t_{½\lambda z}$	Half-life associated with the terminal slope
t_{max}	Time to maximum concentration
U	Urine
US	United States
V_z	Volume of distribution based on the terminal phase
V_{ss}	Volume of distribution at steady state
VIP	Visual Infusion Phlebitis

1. INTRODUCTION

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

1.1 Background

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, which carry out the final steps in cell wall biosynthesis.

The safety pharmacology program assessed the central nervous system, 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 program. In vitro human ether-à-go-go-related gene and dog Purkinje fibers 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, convulsions or proconvulsive behavior has not been seen in subjects.

Nonclinical absorption, distribution, metabolism, and excretion studies did not raise any significant issues that adversely impacted on the development of ceftaroline fosamil. Ceftaroline fosamil and/or metabolites were rapidly distributed throughout the body following single doses of radiolabelled ceftaroline fosamil to 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 dosing of [^{14}C] ceftaroline fosamil of 14 days in rats, the highest concentration of radioactivity was detected in the kidney followed by the skin. Radioactivity concentrations in other tissues were lower than those observed in plasma.

Following a single intravenous (iv) dose of [^{14}C] ceftaroline fosamil to rats and monkeys, the dose was excreted in urine predominantly as ceftaroline and its open-ring metabolite, ceftaroline M-1. Only a very small amount (less than 1%) of ceftaroline fosamil was excreted in the urine of monkeys, while 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 tested. 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.

The nonclinical safety program assessed the toxicity of ceftaroline fosamil and the active component, ceftaroline, in the rat and monkey administered for up to 3 months. The primary toxicities observed were renal toxicity, convulsions, and reactions at the injection site. These findings are also commonly observed both preclinically and clinically with other iv administered cephalosporins. Changes in the kidney included collecting duct hypertrophy or vacuolation, deposition of foreign material associated with granuloma formation, and associated pyelitis. The renal changes tended to recover following 4-week nondosing periods in the rat and monkey and, furthermore, there was no obvious compromise of kidney function. There was some evidence of inflammation at the injection site in repeated-dose studies in rats but not in monkeys. It is noteworthy that the clinical preparation contains L-arginine, which is a known irritant. However, in rabbit studies using this preparation, venous or muscular irritation was not a major concern. Furthermore, although injection site reactions are present at a low level, clinical studies have not had a significant issue with local irritation.

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

The clinical development program for ceftaroline fosamil is comprised of 17 clinical studies, including 2 Phase III cSSSI and 2 Phase III CABP safety and efficacy clinical studies. Approximately 1700 subjects have received ceftaroline as a part of this program. At the recommended dosing regimen of 600 mg ceftaroline fosamil administered as a 60-minute iv infusion every 12 hours for 5 to 14 days for treatment of cSSSI and 5 to 7 days for treatment of CABP, ceftaroline fosamil was well tolerated and demonstrated a favorable safety profile that was compatible with treatment of cSSSI and CABP and known cephalosporin class effects.

The FDA has agreed to a reduced dosage adjustment in patients with moderate (creatinine clearance [CrCL] of greater than 30 to 50 mL/min or less) or severe (CrCL of 15 mL/min or more to 30 mL/min or less) renal impairment and in patients with ESRD (CrCL less than 15 mL/min) as calculated using the Cockcroft-Gault formula. These dose adjustments are as follows:

- Moderate renal impairment: 400 mg ceftaroline fosamil infused over 1 hour every 12 hours
- Severe renal impairment: 300 mg ceftaroline fosamil infused over 1 hour
- End-stage renal disease: 200 mg ceftaroline fosamil infused over 1 hour

The incidences of adverse events (AEs) experienced by subjects receiving ceftaroline fosamil were similar compared with those experienced by subjects receiving comparator therapies. The majority of the AEs experienced were mild or moderate in severity and were assessed as unrelated to ceftaroline fosamil administration. Furthermore, the incidences of death, serious AEs (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 reveal that potential adverse cardiac, renal, or hepatic effects observed 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 seroconversion from a negative to a positive direct Coombs' test were higher in the ceftaroline group compared with the comparator groups, no subject was identified with clinical findings or laboratory results that were consistent with hemolytic anaemia. The incidence of potential antibiotic-associated diarrhea (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 study drug or from the study due to AEs of diarrhea in both treatment groups. Confirmed cases of *Clostridium difficile*-associated diarrhea were rare in both treatment groups.

At the clinical dosages of ceftaroline fosamil studied (600 mg iv every 12 hours or 400 mg iv every 12 hours given as 60-minute infusions), ceftaroline demonstrated an acceptable safety profile that was compatible with treatment of cSSSI and CABP. In addition, no safety concerns were identified in the safety review beyond those already known to be cephalosporin class effects.

The cumulative clinical experience with ceftaroline identified the following adverse reactions:

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, anemia
Nervous system disorders	Headache, dizziness
Gastrointestinal disorders	Diarrhea, nausea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria
Vascular disorders	Phlebitis
Immune system disorders	Hypersensitivity or anaphylaxis
Infections and infestations	*Clostridium difficile* colitis
Investigations	Increased blood creatinine and transaminases, prolonged prothrombin time, international normalized ratio increased, positive direct Coombs
General disorders and administrative site conditions	Infusion site reactions, erythema, pain, phlebitis, pyrexia

This information appears in Table 10-1 of the Investigator Brochure.

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

- Rapid conversion of the prodrug, ceftaroline fosamil, by phosphatases to active ceftaroline in plasma
- Low human plasma protein binding (approximately 20%) of ceftaroline with no distribution into erythrocytes
- Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve increase approximately proportionally to dose (50 to 1000 mg), with a terminal half-life ($t_{1/2}$) of 2 to 3 hours
- Metabolized by opening of ceftaroline's β-lactam ring to ceftaroline, the microbiologically inactive metabolite M-1, and additional minor unidentified metabolites
- No inhibition or induction of cytochrome P450 (CYP450) isoenzymes in vitro
- No metabolism by CYP450 isoenzymes in vitro
- No accumulation or time-dependent PK observed after repeated doses every 12 hours

- Eliminated mainly through renal excretion (clearance is approximately equivalent to the glomerular filtration rate)
- Ceftaroline is not a substrate or inhibitor of human active renal uptake transporters, organic cation transporter-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 fecal intestinal flora
- No dose adjustment needed based on gender, age, or mild renal impairment

For further information, please refer to the Investigator Brochure.

The Sponsor will immediately notify the Principal Investigator if any relevant new safety or toxicology information becomes available during the study.

1.2 Rationale for conducting this study

Part A of this study will evaluate the local tolerability of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted into various infusion volumes (50 mL and 250 mL or 100 mL) and infused every 12 hours into the same vein over 60 minutes, for a maximum of 72 hours (6 infusions). The results from this part of the study will provide clinical data on the tolerability using infusion volumes lower than the 250 mL previously studied in clinical trials.

Part B of the study will be conducted to characterize the single-dose PK of ceftaroline, its prodrug (ceftaroline fosamil), and metabolite (ceftaroline M-1) at the same infusion regimens/volumes as the active treatments in Part A (600 mg ceftaroline diluted in volumes of 50 mL [or 100-mL] and 250 mL). As the dose and infusion duration will remain the same in all treatments, the exposure profiles are expected to be similar across treatments.

1.3 Benefit/risk and ethical assessment

This study will not provide any direct medical benefits to volunteers who participate. The major risk for volunteers who participate in the study is from AEs induced by ceftaroline and the risks associated with iv access.

The potential AEs that may occur with the use of ceftaroline in humans should be evaluated in the context of known cephalosporin-class AEs. Typical class effects include hypersensitivity and allergic reactions, nausea, diarrhea including *C. difficile* colitis, skin rash, leukopenia, thrombocytopenia, eosinophilia, positive Coombs' test, abnormal coagulation, and elevation

of hepatic enzymes. These effects are generally transient and spontaneously reversible after administration of the cephalosporin has been stopped. Severe reactions to cephalosporins including seizures, nephrotoxicity, hemolytic anemia, severe cutaneous reactions, anaphylaxis, and death are infrequent.

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

The incidence of subjects with infusion site reactions during the Phase III studies (cSSSI and CAP combined) was 2.2% for Ceftaroline and 1.6% for comparators. The following infusion site reactions were reported at an incidence up to 0.5% each during ceftaroline treatment: erythema, pain, phlebitis, extravasation, swelling, pruritus and thrombosis.

In a healthy volunteer Phase I study (study P903-01), ceftaroline fosamil was administered in single doses of up to 1000 mg and multiple doses of up to 800 mg. These were given in volumes of 140 mL and infused over 60 minutes. Adverse events related to the injection site (injection site pain/discomfort/thrombophlebitis) were seen in 44% of volunteers who were on active drug. The events were mild in severity. In another healthy volunteer Phase I study (study P903-20), ceftaroline fosamil was administered in single doses of up to 2000 mg and multiple doses of up to 600 mg. These were given in volumes of 250 mL and infused over 60 minutes. One of 16 volunteers on the single dose and 2 of 8 volunteers on the multiple dose had a mild AE related to the infusion site.

Monitoring will be performed according to Good Clinical Practice (GCP) and guidelines of the International Conference on Harmonization (ICH). Additionally, the AEs of hemolytic anemia, acute renal failure, seizure/convulsions, and drug-induced liver injury are currently classified as important potential risks for ceftaroline in the global and EU Patient Risk Management Plan. If 1 of these 4 aforementioned AEs occurs, irrespective of seriousness, the AstraZeneca Patient Safety Physician should be contacted in a timely manner to ensure appropriate data collection for proper safety evaluation.

Clinical laboratory, electrocardiogram (ECG), and vital sign results for volunteers in this study will be monitored and clinically significant abnormalities will be reviewed and assessed by the Investigator. Infusion site reactions (ISRs) will be monitored closely and volunteers who experience infusion site phlebitis will have their infusions discontinued.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of Part A of the study is to evaluate the local tolerability of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions).

The primary objective of Part B is to characterize the PK of ceftaroline in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes.

2.2 Secondary objectives

The secondary objective of Part A of the study is to evaluate the safety of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions).

The secondary objectives of Part B are:

- To characterize the PK of ceftaroline fosamil (the prodrug of ceftaroline) and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes

- To evaluate the safety and tolerability of ceftaroline in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes

3. STUDY PLAN AND PROCEDURES

This CSP has been subject to a peer review according to AstraZeneca standard procedures.

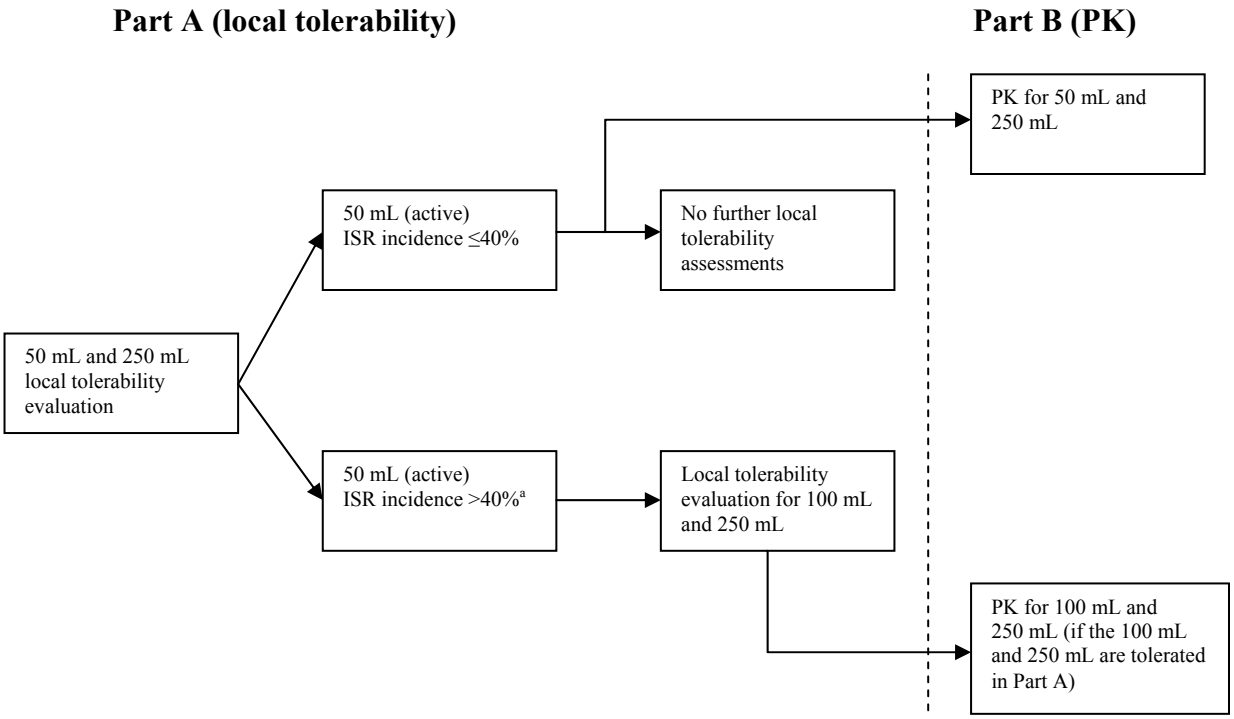
3.1 Overall study design and flow chart

This is a Phase I, single-center, 2-part, randomized study to assess the local tolerability, safety, and PK of ceftaroline in healthy male and female adult volunteers, aged 18 to 75 years, inclusive. Part A will utilitze a placebo-controlled, double-blind, multiple-dose, 2-way crossover design to assess the local tolerability of ceftaroline following multiple infusions of ceftaroline fosamil 600 mg and placebo, each in 50-mL and 250-mL infusion volumes. If the subjects receiving the active 50-mL infusion volume have an incidence of infusion site reactions of >40%, Part A may be repeated using 100-mL and 250-mL infusion volumes. The decision will be made following discussion between the Investigator and the Sponsor and will be based on review of the 50 mL, 250 mL (and corresponding placebo) data (see Section 5.8 for details). Part B will be conducted following Part A and will utilize an open-label, single-dose, 2-way crossover design to evaluate the PK of ceftaroline in either 50-mL and 250-mL

infusion volumes or 100-mL and 250-mL infusion volumes, depending on the local tolerability results from Part A.

A flow chart for the overall study design is presented in Figure 1.

Figure 1 Overall study flow chart



ISR = Infusion site reaction (ie local reaction with a visual infusion phlebitis score of 2 or greater)
For detailed procedures in data review and stopping criteria, see Section 5.8.

a Whether 100 mL investigation is progressed will be based on a review of the 50 mL data compared to the 250 mL and corresponding placebo arms and discussion between Sponsor and Investigator.

3.1.1 Part A

Part A of the study is randomized, placebo-controlled, double-blinded, and a 2-way crossover design to minimize bias. Infusion volumes of 50 mL and 250 mL will be studied to facilitate the identification of effects related to the administration of drug diluted in various infusion volumes rather than the study procedures or situations. Initially, 32 volunteers will be enrolled to ensure at least 24 evaluable volunteers. An additional 32 volunteers may be recruited and dosed to compare a 100-mL infusion volume against the 250-mL infusion volume, based on the incidence of ISRs following the 50-mL infusion.

Tolerability will be deterimined by clinical evaluation of the subjects. Detailed procedures for data review and stopping criteria are described in Section 5.8. If the incidence of ISRs in the

active 50 mL subjects is deemed acceptable (≤40%), then the comparison of the 100-mL infusion volume will not be made to the 250-mL standard (reference) volume. If the 50-mL infusion volume study results indicate the incidence of ISRs is >40%, as detailed in Section 5.8, then the study may be repeated with a comparison of a 100-mL infusion against the 250-mL standard (reference) volume.

Investigational product (IP) will be administered as simultaneous, bilateral, 60-minute infusions every 12 hours over 72 hours (6 infusions) followed by a washout of at least 4.5 days (approximately 108 hours) and another simultaneous, bilateral, 60-minute infusion (in different veins than used previously) every 12 hours over 72 hours (6 infusions). The following treatments will be administered in Part A:

- Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume
- Treatment B: placebo in 50 mL infusion volume
- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume
- Treatment D: placebo in 250 mL infusion volume

On Day 1, volunteers will be randomly assigned in a 1:1 fashion to 1 of 2 treatment sequences of various infusion volumes of ceftaroline fosamil 600 mg and placebo as detailed in Section 5.2. These sequences will avoid administering active treatment in the same arm for both treatment periods and will also avoid administering the same volume to both arms within the same treatment period.

If the active 50-mL infusion subjects have an incidence of ISRs of >40%, the following treatments may be administered (see Section 5.8):

- Treatment E: 600 mg ceftaroline fosamil in 100 mL infusion volume
- Treatment F: placebo in 100 mL infusion volume

This part of the study consists of a 28-day maximum screening period, followed by 2 residential periods of 5 days each separated by a washout of at least 4.5 days (approximately 108 hours), and concludes with a follow-up visit 5 to 10 days after the volunteer is discharged from the final period.

Volunteers will undergo screening assessments during the 28-day period preceding administration of the first infusion of IP. The study assessments and their timings for Part A are outlined in Table 2. Volunteers who meet eligibility criteria will be asked to return to the unit the day before the administration of the first infusion of IP (Day -1) and additional assessments will be performed to ensure they continue to meet the eligibility criteria before beginning each residential period.

For the first infusion of each period, local tolerability will be assessed at predose and at 20, 40, and 60 minutes, 6 hours, and 12 hours after the start of the infusion; the 12-hour assessment will be conducted prior to start of the second infusion. For the subsequent second to sixth infusions, local tolerability will be assessed at 20, 40, and 60 minutes, 6 hours, and 12 hours after the start of the infusion; the 12-hour assessment will be conducted prior to the start of the following infusion.

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. Safety assessments including physical examinations, laboratory assessments, 12-lead ECGs, and vital sign measurements will be performed according to the schedule in Table 2. The study flow chart for Part A is shown below in Figure 2.

Figure 2 Study flow chart for Part A

Visit 1[a] Screening	Visit 2 (Residential period 1)			Visit 3 (Residential period 2)		Visit 4 Follow-up
	Admission	simultaneous bilateral infusions	Washout	Admission	simultaneous bilateral infusions	
	Confirm eligibility and baseline assessments; enroll up to 32 healthy volunteers (24 to complete)	Dosing every 12 hours (6 infusions) on Days 1-3, discharge on Day 4		Confirm eligibility and baseline assessments	Dosing every 12 hours (6 infusions) on Days 1-3, discharge on Day 4	
≤28 days	Day -1	Days 1-4	≥4.5 days[b]	Day -1	Days 1 to 4	5-10 days after final discharge

a Visit 1 may be conducted over 1 or more days during the screening period.
b A minimum washout between treatments of at least 4.5 days (approximately 108 hours). The washout period may be extended if required for resolution of any ISRs experienced by a volunteer in the first treatment period.

Table 2 Table of assessments for Part A

Visit	1	2 and 3 (Residential periods 1 and 2[a])				4
Assessments	**Screening**	**Admission**	**Simultaneous bilateral infusions**			**Discharge[b]**	**Follow-up**
Days	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**(5-10 days after final discharge)**
Informed consent[c]	**X**						
Inclusion/exclusion criteria	X	X					
Demography	X						
Medical/surgical and smoking history	X						
Prior/concomitant medication	X	X	X	X	X	X	X
Complete physical examination	X	X				X	
Supine blood pressure and pulse[d]	X	X	X	X	X	X	X
Height/weight and BMI calculation[e]	X					X	X
12-Lead ECG[f]	X	X				X	
Clinical chemistry/hematology/ urinalysis[g]	X	X				X	X
Viral serology	X						
Estimate creatinine clearance[h]	X					X	
Alcohol, cotinine and urine drug screening	X	X					
Serum/urine pregnancy test[i]	X	X					
FSH[j]	X						
Randomization[k]			X				
Administer dose[l]			X	X	X		
Vascular access site assessments[m]			X	X	X	X	
Record AEs/SAEs[n]	X	X	X	X	X	X	X

AE adverse event; BMI body mass index; ECG electrocardiogram; FSH follicle-stimulating hormone; SAE serious adverse event.

a Volunteers will be admitted for 2 indentical treatment periods. Period 1 and 2 will be separated by a minimum washout period of 4.5 days (approximately 108 hours) between treatments. The washout may be extended at the discretion of the Investigator) if required for resolution of any ISRs experienced by a subject in the first treatment period.

b Volunteers will be discharged on Day 4 following completion of assessments.

c Informed consent will be collected prior to any procedures being performed.

d Supine blood pressure and pulse will be evaluated after the volunteer has rested in the supine position for at least 10 minutes prior to the evaluation. If possible, the same arm and equipment should be used for each evaluation. On Days 1 to 3, blood pressure and pulse will be evaluated in the morning prior to infusion.

e Height/weight will be evaluated and BMI calculated at the screening visit. Only weight will be evaluated upon discharge and follow-up

f A 12-lead ECG will be performed after the volunteer has rested in the supine position for 10 minutes prior to the evaluation.

g The volunteer will fast for at least 4 hours prior to clinical laboratory evaluations.

h Creatinine clearance will be estimated using the Cockcroft-Gault formula at screening and discharge.

i A serum pregnancy test will be performed at screening and a urine pregnancy test at all other time points for all women of childbearing potential. If positive, the volunteer is excluded from participation in the study.

j Performed as appropriate to confirm postmenopausal status.

k Volunteers will be randomized in the morning of Day 1, Period 1, just prior to IP administration.

l Crossover periods: The duration of dosing will start at the initial drug infusion and will continue every 12 hours until the volunteer has received multiple infusions up to 72 hours for a total of 6 infusions during each crossover period. Volunteers who experience a Visual Infusion Phlebitis score of 2 or more will not have any further infusions in the affected arm for the treatment period. The infusion in the contralateral arm may continue if the infusion site is healthy.

m Vascular access site review of local tolerability will be performed by viewing in good lighting each of the infusion sites predose and at 20, 40, and 60 minutes, 6 hours, and 12 hours after the start of the infusion; the 12-hour assessment will be conducted prior to start of the second infusion. For the subsequent second to sixth infusions, local tolerability will be assessed at 20, 40, and 60 minutes, 6 hours, and 12 hours after the start of the infusion; the 12-hour assessment will be conducted prior to the start of the following infusion. Assessment will also occur as clinically indicated. A local reaction will be determined as an ISR and will be recorded as an AE when the severity score is 2 or more as measured by the Visual Infusion Phlebitis scale included in Appendix D.

n SAEs will be collected from the time when informed consent is signed until the follow-up visit. Non-serious AEs will be collected from Day -1 of Period 1 until the follow-up visit.

3.1.2 Part B

Part B will be conducted following a review of the local tolerability and safety results from Part A. The doses to be used in Part B of the study will be determined following review of the Part A data. If the volunteers receiving the active 600 mg diluted in 50 mL have an ISR ≤40% during Part A, then Part B will include single doses of the following:

- Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume
- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)

Depending on the results from Part A, the alternative single doses of treatment shown below may be administered in Part B (see Section 5.8):

- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)
- Treatment E: 600 mg ceftaroline fosamil in 100 mL infusion volume

A total of 10 volunteers will be enrolled into Part B in order to have 8 evaluable volunteers. Volunteers who are randomized in Part A will not be allowed to enroll in Part B. Part B of the study will consist of a screening period of up to 28 days, a 5-day/4-night residential period, and a follow-up period of 5 to 10 days after discharge from the unit. After the screening period, volunteers who qualify will be asked to return for admission to the study center on Day -1 and will remain confined until discharge. On Day 1, volunteers will be randomly assigned in a 1:1 fashion to either treatment sequence CA or AC (or sequence CE or EC if applicable). The arm infused will switch from the first period to the second and thus the randomization will be stratified by the ordering of infusion (Right-Left and Left-Right), to balance any potential arm effects, and to avoid confounding arm with period effects. A single dose of 600 mg ceftaroline fosamil from the appropriate treatment will be administered intravenously over 60 minutes on Day 1. Following a 1-day washout (Day 2), a single dose of 600 mg ceftaroline fosamil from the appropriate treatment will be administered intravenously over 60 minutes on Day 3. Volunteers will be discharged from the unit on day 4 after collection of the 24-hour PK sample and completion of all scheduled assessments.

Plasma PK sample collection and safety assessments including physical examinations, laboratory assessments, 12-lead ECGs, and vital sign measurements will be performed according to the schedule in Table 3. The study flow chart for Part B is shown below in Figure 3.

Figure 3 Study flow chart for Part B

Visit 1[a]	Visit 2					Visit 3
Screening	Residential period					Follow-up
	Admission	Crossover Period 1	Washout	Crossover Period 2	Discharge	
	Confirm eligibility; 10 volunteers to be enrolled	Single-dose administration		Single-dose administration	End of clinic safety assessments	
≤28 days	Day -1	Day 1	Day 2	Day 3	Day 4	5-10 days after clinic discharge

[a] Visit 1 may be conducted over 1 or more days during the screening period.

Table 3 Table of assessments for Part B

Assessments	Visit	1	2 (Residential)					3
		Screening	Check-in	Crossover period 1	Washout	Crossover period 2	Discharge[a]	Follow-up
	Days	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	(5-10 days after discharge)
Informed consent[b]		X						
Inclusion/exclusion criteria		X	X					
Demography		X						
Medical/surgical and smoking history		X						
Prior/concomitant medication		X	X	X	X	X	X	X
Complete physical examination[c]		X	X				X	
Brief physical examination[d]					X			
Supine blood pressure and pulse[e]		X	X	X	X	X	X	X
Height/weight and BMI calculation[f]		X						X
12-Lead ECG[g]		X	X				X	
Clinical Chemistry/hematology/urinalysis[h]		X	X				X	X
Viral serology		X						
Estimate creatinine clearance[i]		X					X	
Alcohol, cotinine, and urine drug screening		X	X					
Pregnancy test[j]		X	X					
FSH[k]		X						
Randomization[l]				X				
Administer dose[m]				X		X		
Pharmacokinetic samples[n]				X	X	X	X	
Record AEs/SAEs[o]		X	X	X	X	X	X	X

AE adverse event; BMI body mass index; ECG electrocardiogram; FSH follicle-stimulating hormone; SAE serious adverse event.

a Volunteers will be discharged on Day 4 after completion of assessments

b Informed consent will be collected prior to any procedures being performed.

c A complete physical examination will be performed at screening, Day -1, and discharge and includes an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

d A brief physical examination will be performed on Day 2 and includes an assessment of the general appearance, abdomen, lungs, and the cardiovascular systems.

e Supine blood pressure and pulse will be evaluated after the volunteer has rested in the supine position for at least 10 minutes prior to the evaluation. If possible, the same arm and equipment should be used for each evaluation. While in residence, blood pressure and pulse will be evaluated in the morning (prior to dosing on Days 1 and 3).

f Height/weight will be evaluated and BMI calculated at the screening visit. Only weight will be evaluated upon follow-up.

g A 12-lead ECG will be performed after the volunteer has rested in the supine position for 10 minutes prior to the evaluation.

h The volunteer will fast for at least 4 hours prior to clinical laboratory evaluations.

i Creatinine clearance will be estimated using the Cockcroft-Gault formula at screening and discharge.

j A serum pregnancy test at screening and a urine pregnancy test on Day -1 will be performed for all women of childbearing potential. If positive, the volunteer is excluded from participation in the study.

k Performed as appropriate to confirm postmenopausal status.

l Volunteers will be randomized in the morning of Day 1 just prior to IP administration.

m Crossover periods: Volunteers will receive a single, 60-minute infusion in each crossover period.

n Pharmacokinetic blood samples will be collected contralaterally from the dosing arm and appropriately processed at the following time points relative to the start of the infusion, unless otherwise indicated: predose (-60 to 0 minutes prior to the start of the iv infusion), 20 minutes, 40 minutes, end of infusion (within 2 minutes before the end of the infusion), 65 minutes, 75 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 18 hours and 24 hours postdose.

o SAEs will be collected from the time when informed consent is signed until the follow-up visit. Non-serious AEs will be collected from Day -1 of Period 1 until the follow-up visit.

3.2 Rationale for study design, doses and control groups

Ceftaroline fosamil 600 mg has been approved in the US and has been submitted to the European Medicines Agency for approval. To support 600 mg to be administered in a volume less than the standard 250 mL, Part A of this study is being carried out to look at local tolerability when diluted in lower volumes.

Part B of the study will be conducted to characterize the single-dose PK of ceftaroline, its prodrug (ceftaroline fosamil), and metabolite (ceftaroline M-1) at the same infusion regimens/volumes as the active treatments in Part A (600 mg ceftaroline diluted in volumes of either 50 mL and 250 mL, or 100 mL and 250 mL, as described in Section 5.8).

This study will be conducted in healthy adult volunteers to avoid interference from disease process or other drugs. The selection criteria are defined such that volunteers selected for participation in the study are known to be free from other clinically significant illness and have adequate veins on the back of both hands and both forearms to accommodate the simultaneous bilateral infusions for Part A.

This study will be conducted in 2 parts, customized to the respective primary objectives. The crossover design for both study parts allows each volunteer to be his/her own reference, as well as accounting for period effects, if they exist. The duration of the infusion administration period is to follow established practice guidelines which recommend that peripheral IV sites should be changed every 72 hours. A minimum one day washout (used in Part B) is sufficient considering ceftaroline t½ of approximately 2 to 3 hours. The washout period in Part A has been designed as a minimum of 4.5 days (approximately 108 hours) between treatments to allow any ISRs experienced by a subject in Period 1 to resolve prior to treatment in Period 2.

As the assessments for the primary PK objective are not subjectively biased, an open-label design for Part B is appropriate. In addition, an open-label design has the advantages of minimizing discomfort to the volunteers and reducing the number of PK samples associated with bilateral administrations of the active and placebo treatments required to maintain the blind of the different volumes being infused. The randomization will also be stratified by arm to avoid confounding arm with period effects and to reduce the potential for carryover effects due to ISRs or PK sampling.

To date, infusion volumes ranging from 175 mL to 270 mL have been used in the Phase I, II and III trials. All Phase III studies for both the cSSTI and CAP programs have only used a standard dose of 600 mg for subjects with normal or mild renal impairment and a dose of 400 mg for those with moderate renal impairment at concentrations ranging from of 1.5 to 2.7 mg/mL for the intravenous (iv) infusion solutions. However since doses used in the Phase 1 studies have varied more, the iv infusion concentrations administered have ranged from 0.3 to 8 mg/mL. The concentrations to be used in the current study are 2.4 mg/mL (250 mL volume), 12 mg/mL (50 mL volume), and if required, 6 mg/mL (100 mL volume).

Three studies in the rabbit to assess local tolerance were dosed using a concentrations of 4.2 mg/mL administered in the ear vein or 150 and 200 mg/mL administered intramuscularly.

In the 4-week monkey study (TAK599-00037) and 13-week rat and monkey studies (P0903-T-010 and P0903-T-011, respectively) the severity and incidence of microscopic findings at the infusion sites was similar across all groups, including controls, both at the end of the main test phase and at the end of the recovery phase. The high-dose groups had were administered ceftaroline fosamil intravenously in concentrations of ceftaroline fosamil exceeding 12 mg/mL. Importantly, monkeys in the 4-week study were administered ceftaroline fosamil as 1-hour infusion into the saphenous or cephalic vein with no suggestion of major irritation issues in concentrations up to 80 mg/mL. In these studies, there was no evidence of haemolysis from haematology raw data.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the volunteer screening log, of volunteers who entered prestudy screening.

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

4.1 Inclusion criteria

For inclusion in the study volunteers should fulfill the following criteria:

1. Provision of informed consent prior to any study-specific procedures

2. Healthy male and/or female volunteers between the ages of 18 to 75 years, inclusive, with veins on the back of both hands and both forearms suitable for cannulation or repeated venipuncture. For Part A, volunteers must be willing to have both arms used during the study with catheters inserted for up to a maximum of 72 hours (6 infusions).

3. 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

4. Male volunteers must be willing to use barrier contraception ie, condoms, from the first day of dosing until 3 months after the last dose of IP.

5. Have a body mass index (BMI) between 18 and 30 kg/m^2, inclusive, and weigh at least 50 kg

6. As judged by the Investigator, able to understand and be willing to communicate with the Investigator and comply with all the study requirements

4.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to AstraZeneca, Cerexa, Forest employees, their close relatives, and/or staff at the study site)

2. Previous randomization to treatment sequence in the present study

3. Use of any other investigational compound or participation in another clinical trial, within 3 months prior to first administration of IP in this study. The period of exclusion begins at the time of the last visit of the prior study. Volunteers consented and screened but not dosed in this study or previous Phase I studies are not excluded.

4. History of any clinically significant disease or disorder, eg, cardiac, neurological, hematological, psychiatric, gastrointestinal, hepatic, renal disease, or other condition which, in the opinion of the Investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study

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

6. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IP

7. Any clinically significant abnormalities in the physical examination, laboratory values, or 12-lead ECG, as judged by the Investigator

8. Abnormal vital signs, after 10 minutes supine rest, defined as any of the following:

   - Systolic blood pressure >140 mm Hg
   - Diastolic blood pressure >90 mm Hg

9. Any positive serology result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV), or human immunodeficiency virus (HIV)

10. Known or suspected history of drug abuse, as judged by the Investigator

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

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

13. Positive screen for drugs of abuse, or cotinine (nicotine) at screening or positive screen for drugs of abuse, alcohol or cotinine on admission to the unit prior to the first administration of IP

14. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of any hypersensitivity or allergic reaction to any β-lactam antimicrobials or drugs with a similar chemical structure or class as ceftaroline

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

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

17. For Part B, plasma donation, or any blood donation, blood product donation, or blood loss greater than 500 mL during the 3 months prior to screening

18. Creatinine clearance of less than 80 mL/minute (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 in mg/dL

19. Judgement by the Investigator that the volunteer 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.

Procedures for withdrawal of incorrectly-enrolled volunteers are presented in 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 clinical laboratory evaluations

2. Eat and drink only the standardized meals and drinks provided (apart from water) during the residential periods in the unit

3. Abstain from consuming any of the following:

   - Alcohol from 72 hours before admission to the clinic, during each residential period, and for 72 hours before the study follow-up visit

   - Energy drinks containing taurine or glucuronolactone, eg, Red Bull from 72 hours before admission, during each residential period, and for 72 hours before the study follow-up visit

   - Caffeine- and xanthine-containing food and drink from 48 hours prior to infusion of the first dose and during each residential period, apart from any provided as part of a standardized meal. Excessive intake of caffeine should be avoided during the washout period (Part A) and between discharge from the unit and the study follow-up visit.

   - Poppy seeds found in specialty breads from time of consent until after the final medical examination at the study follow-up visit

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

5. Abstain from taking any medication, prescribed or over-the-counter products (other than paracetamol/acetaminophen or hormone replacement therapy), from 2 weeks prior to the first administration of IP until after the final medical examination at study 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.

6. Volunteers should refrain from strenuous physical activity, which is not within the volunteers' normal daily routine, from 7 days prior to first admission to the unit until after the final medical examination at the study follow-up visit

7. Volunteers participating in Part B of the study should abstain from blood or plasma donation from 3 months before screening until 3 months after screening

8. Male volunteers should use a condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm or fathering a child from the date of dosing until 3 months after dosing with the IP; 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. 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.

9. Remain in the unit during each residential period until all study assessments and procedures have been completed including completion of the 72-hour infusions (sixth final infusion set in Period 2) for Part A and collection of the 24-hour PK sample for Part B

5.2 Subject enrollment and randomization

The Investigator will:

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

2. Assign potential volunteer a unique enrollment number, beginning with 'E0001001'

3. Determine volunteer eligibility. See Sections 4.1 and 4.2.

4. Assign eligible volunteers a unique subject number, beginning with '1001'

If a volunteer withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

Procedures for randomization

Randomization schemes will be produced for each study part separately by using the global randomization system. Randomization will be performed on Day 1 just before administration of the IP. Randomization codes will be assigned strictly sequentially as volunteers become eligible for randomization.

For Part A, volunteers will be randomly assigned in a 1:1 fashion to 1 of 2 treatment sequences (to Sequence 1 or 2 or, in the event the 50-mL infusion volume is deemed poorly tolerated, to Sequence 3 or 4) of infusion volumes of ceftaroline fosamil 600 mg and placebo,

as outlined in Table 4 (see Section 3.1.1). These sequences avoid administering active treatment in the same arm for both treatment periods and administering the same volume to both arms within the same treatment period.

Table 4 Treatment arm randomization scheme

Sequence	Crossover period	Left arm	Right arm
Sequence 1	1	50 mL active (Treatment A)	250 mL placebo (Treatment D)
	2	50 mL placebo (Treatment B)	250 mL active (Treatment C)
Sequence 2	1	250 mL active (Treatment C)	50 mL placebo (Treatment B)
	2	250 mL placebo (Treatment D)	50 mL active (Treatment A)
Sequence 3	1	100 mL active (Treatment E)	250 mL placebo (Treatment D)
	2	100 mL placebo (Treatment F)	250 mL active (Treatment C)
Sequence 4	1	250 mL active (Treatment C)	100 mL placebo (Treatment F)
	2	250 mL placebo (Treatment D)	100 mL active (Treatment E)

Sequence 3 and Sequence 4 are conditional, as described in Section 3.1.1.

For Part B volunteers will be randomly assigned in a 1:1 fashion to either treatment sequence CA or AC. If Treatment A is shown to be poorly tolerated in Part A of the study, Treatment E will replace Treatment A in Part B, and the volunteers will be randomized 1:1 to treatment sequence CE or EC. The arm infused will switch from the first period to the second and thus the randomization will be stratified by the ordering of infusion (RL and LR), to balance any potential arm effects, and to avoid confounding arm with period effects.

5.3 Procedures for handling subjects incorrectly randomized

Volunteers who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

Where a subject, who does not meet the selection criteria, is randomised in error and this is identified before dosing, the subject should be withdrawn from the study. A discussion should occur between the CPA Physician and the Investigator regarding whether a replacement may be considered. The CPA Physician is to ensure all such decisions are appropriately documented.

Where subjects are enrolled but subsequently fail to meet the study criteria post initiation, a discussion should occur between the CPA Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

If a subject is withdrawn from study drug they should be advised to continue assessments for safety monitoring.

The CPA Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the volunteer should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Part A of this study is double-blind with regard to treatment (ceftaroline or placebo). The following personnel will have access to the randomization list:

- The AstraZeneca personnel carrying out the labeling and packaging of IP
- The pharmacy personnel preparing IP at the site

The randomization 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 and tubing will be amber colored to maintain the blind.

Part B is open-label; therefore, no blinding procedures are needed.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized volunteer, will be available to the Investigator or pharmacist at the study center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the volunteer requires knowledge of the treatment randomization. The Investigator documents and reports the action to the Sponsors, without revealing the treatment given to the volunteer to the Sponsors' staff. Following completion of Part A, an unblinded review of the ISR incidence will be performed, as described in Section 5.8.

The Sponsors retain the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data (other than as described in Section 5.8) until all decisions on the evaluability of the data from each individual volunteer have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Ceftaroline fosamil	600 mg of ceftaroline fosamil a pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20 mL vial	

The formulation number and batch numbers will be recorded in the Study Master File and identified in the CSR.

Ceftaroline fosamil for infusion is supplied as 600 mg of ceftaroline fosamil (the prodrug of ceftaroline), a sterile pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20-mLvial. An excipient, L-arginine (approximately 660 mg L-arginine/g of prodrug) is added as an alkalizing agent to maintain the pH of the constituted solution to pH 4.8 to 6.2. The investigational site will be responsible for diluting the concentrate to obtain the desired infusion volume.

Placebo for Part A will consist of 0.9% sodium chloride infusion fluid of various infusion volumes (ie, 50, 100, or 250 mL) as appropriate.

The constitution time should be no more than 120 seconds. The constituted and diluted ceftaroline fosamil iv solutions should be administered promptly; however, the constituted vial is stable for up to 4 hours at room temperature. Once the constituted vial is diluted in the infusion bag or bottle, it should be administered within 6 hours of the initial constitution or within 24 hours if the bag or bottle is stored in the refrigerator at 2° to 8°C.

Reconstituted solutions and subsequent infusions should be prepared using standard aseptic techniques.

Those individuals involved in the drug-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.

Product preparation requirements

The following will be used to administer study drug:

Ceftaroline:

- Ceftaroline fosamil powder 600 mg containing L-arginine alkalizing agent
- Sterile water for infusion, USP

- 0.9% sodium chloride infusion fluid (50, 100, or 250 mL infusion bags, as appropriate)
- Standard catheters approved for use in both the US and EU

Placebo for Part A will consist of 0.9% sodium chloride infusion fluid (50, 100, or 250 mL infusion bags).

See Table 5 for the constitution of the ceftaroline fosamil and volume to be inserted into infusion bag. The extractable volume of the reconstituted vial should then be transferred to the 0.9% sodium chloride infusion bag to achieve the final bag volume.

Table 5 Concentration and extractable volumes of reconstituted active drug

Active drug	Volume of water required for reconstitution of vial	Extractable volume of reconstituted vial	Solution concentration
Ceftaroline fosamil 600 mg	20.0 mL	20.7 mL	29 mg/mL

Further instructions regarding dose preparation, blinding, and administration will be documented in separate pharmacy handling instructions.

5.5.2 Doses and treatment regimens

During Part A, each volunteer will receive simultaneous bilateral iv infusions of IP (ceftaroline fosamil 600 mg in 1 arm and placebo in the other arm) over 60 minutes every 12 hours for a maximum of 72 hours (6 infusions). Volunteers will then enter a minimum 4.5-day (approximately 108 hours) washout period before crossing over and receiving simultaneous bilateral iv infusions of IP (ceftaroline fosamil 600 mg in the contralateral arm from Period 1 and placebo in the other arm), in veins different than those used previously, over 60 minutes every 12 hours for a maximum of 72 hours (6 infusions). Should the volunteer experience an ISR of 2 or greater as measured by the Visual Infusion Phlebitis (VIP) scale (see Appendix D), the infusion must be stopped on that arm (ie, the cannula will not be resited for that treatment period) and the ISR will be recorded as an AE. The infusion on the other arm will continue, as appropriate. See Section 5.8 for study stopping criteria and Section 3.1.1 for a description of treatments and treatment sequences.

In Part B, each volunteer will receive a single dose of 600 mg ceftaroline fosamil infused over 60 minutes in each crossover period (Days 1 and 3). See Section 3.1.2 for a description of treatments.

Catheters should be standardized and approved for use in both the US and EU. For each crossover portion, catheters should be inserted into the same ‘anatomical site’, preferably hand and forearm, with care taken to minimize cannula placement in the wrist or antecubital fossa.

Cannula insertion must be performed by a qualified health care professional. Aseptic technique must be used and standard precautions observed prior to and during vascular access placement. This includes the appropriate use of hand hygiene, glove selection, glove use, and decontamination of the peripheral catheter site with individually packaged alcohol wipes. Please note, only alcohol wipes are to be used to clean the site of catheter placement. Peripheral vascular access catheter placement will be documented for each volunteer in a separate source document. Information recorded will include batch number, gauge and length, number of attempts, anatomical location, and volunteer's response to placement. Care of the catheter site and restrictions are specified in advance. The mechanics of line clearance post infusion should be carefully considered.

For dosing in both study parts and for all infusions, the date and time of the infusion start and stop as well as the start and stop of any infusion interruption and restart of the infusion, and the actual volume and amount of ceftaroline fosamil infused will be recorded. In addition, the arm (left or right) in which the infusion is administered will be documented.

5.5.3 Additional study drug (not applicable)

5.5.4 Labelling

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

5.5.5 Storage

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

Vials of ceftaroline fosamil for injection dry mixture should be stored at 2° to 8°C until ready for use. Vials should be used before the labeled expiry date.

5.6 Concomitant and poststudy treatment(s)

Apart from paracetamol/acetaminophen and hormone replacement therapy, no concomitant medication or therapy will be allowed. The volunteers 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 volunteer's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the electronic case report form (eCRF). When any medication is required, it should be prescribed by the Investigator who should inform the CPA Physician. Following consultation with the CPA Physician, the Investigator should determine whether or not the volunteer should continue in the study.

5.7 Treatment compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by supervised administration of the IP by the Investigator or delegate. The dose, dates, and times of administration of the IP will be recorded and will be checked by the monitor at monitoring visits.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The study centre personnel will account for all investigational products received at the study center, unused investigational product and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.8 Discontinuation of investigational product and withdrawal from study

Volunteers may be discontinued from IP in the following situations:

- Volunteer decision. The volunteer is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event
- Severe noncompliance to this CSP as judged by the Investigator and/or AstraZeneca
- Randomization in error (see Section 5.3)
- Catheter becomes dislodged or is removed from either arm prior to scheduled time point

Dosing for any individual volunteer will be stopped if the volunteer experiences a possibly drug-related SAE or a possibly drug-related significant nonserious AE, which in the opinion of the Investigator or Sponsor, warrants discontinuation from the study for that volunteer's well being.

Volunteers who have a VIP score of 2 or more will not have any further infusions in the affected arm for that treatment period. For Part A, if the infusion site in the contralateral arm is healthy, the infusions may continue in that arm.

Stopping criteria for Part A

Dosing will stop with an infusion volume (50, 100 or 250 mL) if any of the following scenarios occur with a reasonable possibility of a causal relationship with the investigational product:

- Two or more subjects report a serious adverse event (SAE) or have a VIP score of 5
- Four or more subjects have a VIP score of 4

During Part A of the study data will be reviewed by the Investigator on an ongoing basis. If 15 or more subjects develop ISRs, but the stopping criteria listed above have not been met, the Investigator may request an independent unblinded review of the available safety and tolerability data. If once unblinded the incidence of ISRs on any active volume is >40% of the total anticipated recruitment for Part A, an ad hoc data review meeting will be arranged between the Investigator, Sponsor, and other team members, as applicable, to determine study termination. Otherwise, dosing will be continued as planned in the remaining 50 mL subjects.

At completion of Treatment A (50 mL infusion volume), an unblinded review of the ISR incidence will be performed by a person who is not involved with the conduct of the study. If the cumulative ISR incidence is ≤40% in both active treatments for the 50-mL and 250-mL infusion volume (Treatments A and C) as determined by the unblinded reviewer, the Investigator and Sponsor will be notified, and the study will proceed to Part B. However, if the cumulative ISR is >40% for the 50-mL active treatment (Treatment A) but is ≤40% for the 250-mL active treatment (Treatment C), after review in the context of the corresponding placebo findings and following discussion with the Sponsor, Part A may be repeated with the 100-mL and 250-mL while Part B will be pending until after data review of the last cohort in Part A . In the instance of being repeated with 100 mL, the data review and study termination procedures in Part A will then be applied to the 100-mL treatment. At the completion of the last cohort for the 100-mL and 250-mL evaluation in Part A, if the cumulative ISR is ≤40% in both active treatments for the 100-mL and 250-mL infusion volume (Treatments E and C) as determined by the un-blinded reviewer, the Investigator and Sponsor will be notified, and the study will proceed to Part B which will include Treatment E and Treatment C.

Procedures for discontinuation of a subject from investigational product

Volunteers are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such volunteers will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up. See Sections 6.3.4 and 6.3.5.

Additional volunteers may be enrolled at the discretion of the Sponsor if the number of evaluable volunteers is not sufficient for either study part.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of these assessments are detailed in Table 2 and Table 3 for Parts A and B, respectively.

It is important that PK sampling during Part B occurs as close as possible to the 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. 12-lead ECG

2. Blood pressure and pulse rate

3. PK blood sample (Part B only)

4. Other safety and laboratory assessments

Volunteers will fast for at least 4 hours prior to the clinical laboratory evaluations.

6.1 Recording of data

The Phase I electronic data capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in this CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study center.

6.2 Data collection and enrollment

6.2.1 Screening procedures

For both study parts, each volunteer will undergo screening during the 28 days prior to admission to the study center to confirm eligibility. This will consist of:

- Obtaining written informed consent before starting any study-specific procedures
- Recording of demographic data (date of birth, sex, and race)
- A standard medical, medication, and surgical history as well as smoking history with review of the inclusion and exclusion criteria with the volunteer
- A complete physical examination (see Section 6.3.7)
- Height (in cm), weight (in kg), and calculation of BMI
- Vital signs (resting supine blood pressure and pulse rate)
- Recording a resting 12-lead paper ECG

- Following a minimum 4-hour fast, blood samples will be collected for routine clinical chemistry (including serum pregnancy tests for female subjects and FSH for females only to confirm postmenopausal status), hematology, and screening for HBsAg, HCV, and HIV
- A urine sample for routine urinalysis (including microscopic examination), drugs of abuse screen, alcohol and cotinine screen
- Creatinine clearance estimation
- Concomitant medication use
- Recording of SAEs

After admission and before randomization the Investigator should reassess each volunteer to reconfirm eligibility.

6.2.2 Follow-up procedures

A poststudy medical examination will be performed 5 to 10 days after discharge from the study center (Day 4 of Period 2 for Part A, or Day 4 of Part B). These assessments will include supine blood pressure and pulse; weight; clinical chemistry, hematology, and urinalysis; and recording of concomitant medications and AEs. The volunteers will be fasted for 4 hours prior to follow-up procedures.

6.3 Safety

The Investigator is responsible for ensuring that all staff involved in the study are 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 D. These assessments will occur as specified in Section 3.1.1. 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 D. For those volunteers who experience an ISR, their washout period may be extended beyond 3 days to allow recovery of the infusion site.

6.3.2 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a preexisting 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 and ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.3.3 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the volunteer 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 definition of other significant AE (OAE) see Section 11.1.2.

6.3.4 Recording of adverse events

Time period for collection of adverse events

SAEs will be collected from the time when informed consent is signed until the follow-up visit. Non-serious AEs will be collected from the first admission to the clinical unit until the follow-up visit.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the volunteer's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any volunteer 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:

- Adverse event diagnosis/description
- Date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Adverse event caused volunteer'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 IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

Adverse events based on signs and symptoms

All AEs spontaneously reported by the volunteer or reported in response to an open question from the study personnel eg 'Have you had any health problems since you were last asked?', or revealed by observation will be collected and recorded in the eCRF. 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 summarized in the 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 fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically-relevant deteriorations in nonmandated 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.

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 Investigators or other site personnel inform appropriate AstraZeneca representatives within 1 day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

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

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

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

6.3.6 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the study plan (see Table 2 and Table 3). The date and time of collection of all laboratory tests will be recorded in the appropriate eCRF. Volunteers will fast for 4 hours prior to the clinical laboratory evaluations. Laboratory variables to be measured are shown in Table 6.

Table 6 Safety laboratory variables

Haematology	Clinical chemistry	Urinalysis
Blood (B)-hemoglobin	Serum (S)-albumin	Urine (U)-glucose
B-platelet count	S-alanine aminotransferase	U-hemoglobin
B-absolute leukocyte differential count[a]	S-aspartate aminotransferase	U-protein
B-leukocyte count	S-alkaline phosphatase	Microscopic examination[b]
B-reticulocytes	S-bilirubin, total	
B-erythrocytes	S-calcium, total	
B-hematocrit	S-creatinine	
B-erythrocyte mean cellular volume	S-glucose	
	S-potassium	
	S-sodium	
	S-total protein	

[a] The leukocyte differential count will include: neutrophils, eosinophils, basophils, lymphocytes, and monocytes.
[b] All urine samples will be evaluated microscopically.

Creatinine clearance will be estimated using the Cockcroft-Gault formula (see Section 4.2) at screening and at clinic discharge on Day 4 of Period 2 for Part A and Day 4 for Part B.

Additionally, at screening all volunteers will be tested for HIV, HBsAg, and antibodies to HCV. If indicated for females, FSH will be measured to determine their menopausal status at screening. Urine will be tested for alcohol and drugs of abuse at screening and admission to the study center on Day -1 including amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, phencyclidine, tetrahydrocannabinoid, benzodiazepines, and opiates. Urine will also be screened for cotinine at screening. For female volunteers a serum pregnancy test will be performed at screening and a urine test on each admission to the study center (Day -1).

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Volunteers in whom suspected values of clinical significance are confirmed will either not be included in the study or, if already randomized, will be followed until normalization or for as long as the Investigator considers necessary. Additional laboratory assessments may be performed for safety reasons if judged appropriate by the Investigator.

The safety laboratory samples will be analyzed using routine methods at the local safety laboratory of the study center.

For AEs based on laboratory tests, see Section 6.3.4. For blood volumes, see Section 7.1.

6.3.7 Physical examination

A complete physical examination will be performed at screening, Day -1, and at each clinic discharge and includes an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, respiratory, and neurological systems. During the washout period of Part B, prior to dosing, a brief physical examination is required.

Height will be measured in centimeters and weight in kilograms. Measurements should be taken without shoes and, if possible, the same scale used for all measurements. Body mass index will be calculated from the height and weight at screening.

For AEs based on examinations and tests, see Section 6.3.4.

6.3.8 ECG

A 12-lead resting paper ECG will be recorded on the days indicated in the study plan (Table 2 and Table 3). Volunteers must rest in a supine position for 10 minutes before each assessment. Overall evaluation (normal/abnormal) will be recorded in the eCRF. If the ECG is abnormal, the abnormality and its clinical significance will be specified in the eCRF.

The print-out of the ECG is to be signed, dated, and filed in the Investigator's Study File along with a signed and dated copy (if the print-outs are not on archive-quality paper).

For AEs based on examinations and tests, see Section 6.3.4.

6.3.9 Vital signs

Supine blood pressure and pulse will be measured using noninvasive equipment after the volunteer has rested at least 10 minutes in a supine position. If possible, the same arm and equipment should be used for each evaluation. While in residence, blood pressure and pulse will be evaluated in the morning. For timing of assessments refer to Table 2 and Table 3 for Parts A and B, respectively.

For AEs based on examinations and tests, see Section 6.3.4.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Pharmacokinetic data will be collected in only Part B of this study.

At each time point presented in Table 3, 1 venous blood sample (approximately 4 mL per sample) will be collected contralaterally from the dosing arm for the determination of ceftaroline fosamil (the prodrug of ceftaroline), ceftaroline, and ceftaroline M-1 (the metabolite of ceftaroline) concentrations in plasma.

The sampling date and time will be recorded for all samples. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For blood sample volumes to be collected, 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 will be analyzed by a designated laboratory 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 the time of receipt by the bioanalytical laboratory will be analyzed.

6.5 Pharmacodynamics (Not applicable)

6.6 Pharmacogenetics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each volunteer in this study is presented in Table 7.

Table 7 Volume of blood to be drawn from each subject

			Part A		Part B	
Assessment		**Sample volume (mL)[a]**	**No. of samples**	**Total volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	5	6	30	4	20
	Hematology	2	6	12	4	8
	Serology	3.5	1	3.5	1	3.5
	Serum pregnancy test[b]	3.5	1	3.5	1	3.5
	FSH[b]	3.5	1	3.5	1	3.5
Pharmacokinetic	ceftaroline fosamil, ceftaroline, and ceftaroline M-1	4	0	0	30	120
Total	Males			45.5		151.5
	Females			52.5		158.5

a If a cannula is used, an additional 1 mL of blood will be collected to flush the cannula.
b Female subjects only; FSH will be assessed if indicated to determine volunteer's menopausal status

The number of samples collected, as well as the volume required for each analysis, may be changed during the study as new data on ceftaroline fosamil become available. However, the maximum volume to be drawn from each volunteer will not exceed 450 mL, ie, approximately the same volume as would be drawn during a regular blood donation.

7.2 Handling, storage, and destruction of biological samples

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

7.2.1 Safety samples

Safety samples will be used up, or disposed of after analysis.

7.2.2 Pharmacokinetic and/or pharmacodynamic samples

Samples will be used up, or disposed of after the CSR has been finalized, unless retained for future analyses.

Additonal analyses may 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 reproductibility of the method and will be reported in a separate table in the bioanalytical study contribution 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 of this CSP 'International Airline Transportation Association (IATA) 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not to be shipped and no further samples will be taken from the volunteer 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 lifecycle.

The Investigator keeps full traceability of collected biological samples from the volunteers while in storage at the center 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, disposed of, or until further shipment, and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca bio bank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

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

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site

- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

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

The Ethics Committee 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 volunteers. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any volunteer into the study.

The Ethics Committee should approve all advertising used to recruit volunteers for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the CSP should be reapproved by the Ethics Committee annually.

Before enrollment of any volunteer 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 the Regulatory Authority, Ethics Committee, and Principal Investigator with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

8.4 Informed consent

The Investigator will:

- Ensure that each volunteer is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure that each volunteer is notified that they are free to withdraw from the study at any time
- Ensure that each volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each volunteer 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 volunteer
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

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, 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 Ethics Committee 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 protocol to the Investigator. For distribution to the Ethics Committee see Section 8.3.

If a protocol amendment requires a change to the Informed Consent Form, AstraZeneca and the Ethics Committee 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 Ethics Committee.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, 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, analyzed, and accurately reported according to the CSP, ICH/GCP guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT

9.1 Prestudy activities

Before the first volunteer is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate volunteers for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and the responsibilities of AstraZeneca or their representatives.

9.2 Training of study site personnel

Before the first volunteer is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures.

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 site, including visits to:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the CSP, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the volunteer's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating volunteers. This will require direct access to all original records for each volunteer (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the volunteer's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the volunteer

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center need information and advice about the study conduct.

9.3.1 Source data

The location of data identified as source will be provided in a source data identification document provided by

9.4 Study agreements

The Investigator should comply with all the terms, conditions, and obligations of the CSA or equivalent for this study. In the event of any inconsistency between this CSP and the CSA, the CSP shall prevail with respect to the conduct of the study and the treatment of volunteers and in all other respects, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Investigator should be in place before any study-related procedures can take place or volunteers are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last volunteer undergoing the study'.

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

A 21 CFR part 11 compliant electronic data capture (EDC) system will be used for this study. Electronic CRFs will be produced by for each subject. The majority of study data collected will be either directly entered by clinical research staff or directly captured from devices onto the electronic CRF. Data will be available for AstraZeneca review via predefined reports extracted from the database at agreed intervals. The electronic CRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

When direct data entry onto the electronic CRF is inappropriate or impractical data will be collected on paper source documents and subsequently transcribed, where necessary, onto the electronic CRFs by the clinical research staff . All source documents will be retained by . Photocopies of completed source documents will be provided only if essential (ie, for regulatory purposes) at the request of the AstraZeneca.

Laboratory data are managed within the information management system and only the date and time of sampling are recorded in the electronic CRF. Data that are not directly captured eg, safety laboratory results and AE coding, are managed externally from the main study database. These data will be merged with the data from the main study database in post-production. Datasets supplied to AstraZeneca will contain all study data.

The informed consent will be kept with a copy of the completed source documents in the appropriate file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

All electronic CRF entries, corrections, and alterations must be made by the Investigator or other, authorised, study-site personnel and only by individuals who have received training on the EDC system. Site staff may be allowed access to the system only after training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained

The Data Management Plan will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process.

Validity and consistency of data will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the course of the study. The data management team will raise queries in the EDC system to

resolve discrepancies. The Investigator must verify that all data entries in the electronic CRFs are accurate and correct. After completion of the study and when all collected data is validated, the database will be locked. Final data will be extracted from the EDC system and delivered to AstraZeneca in the form of SAS® datasets in accordance with defined project standards. A portable document format (PDF) copy of the electronic CRF will be produced for each study subject and included in the final delivery.

Adverse event and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary.

The EDC system will keep track of all data entry, alterations and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside with the Dictionary coding.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database. External data reconciliation will be done with the clinical database as applicable.

SAE/AE Reconciliation

Serious Adverse Event Reconciliation Reports are produced and reconciled with the Patient Safety database and/or the Investigational Site.

Data verification and validation

The source data verification will be carried out by a site monitor comparing database entered data to source documents (ie, ECG print-outs, laboratory results and other health records at the study site). Questions and corrections will be noted and verified by the Investigator.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Calculation of change from baseline

Change-from-baseline values will be calculated for the variables listed below, as the posttreatment value minus the value at baseline. The baseline values for both Part A and Part B will be as follows:

- Clinical laboratory tests: Day -1
- Vital signs (supine): Day 1 predose

If a volunteer is missing the baseline collection, the previous nonmissing evaluation will become the baseline value. If no baseline or previous-to-baseline value exist, then the baseline value will be treated as missing and no changes from baseline will be calculated.

11.1.2 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 or AEs leading to discontinuation of IP and withdrawal from the study. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs, and other safety assessments will be performed for identification of OAEs.

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

11.2 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma 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 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 units of hour for PK protocol time points that are in units of minute (including 20-, 40-, 60-, 65-, 75-, and 90-minute plasma PK samples). These derived nominal time points will be rounded to 2 decimal places.

Pharmacokinetic parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 5.2, or higher, (Pharsight Corp., Mountain View, California, US) or SAS® Version 9.2, or higher (SAS Institute Inc., Cary, North Carolina, US). All PK computations will be performed using WinNonlin® Professional Version 5.2, or higher; or SAS® Version 9.2, or higher. Graphics may be prepared with SAS® Version 9.2, or higher; or SigmaPlot® 9.0, or higher (Systat Software Inc., San Jose, California, US).

Where estimable, the following single-dose PK parameters will be calculated for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 from plasma concentrations collected following dosing in each period (Days 1 and 3):

- Maximum plasma concentration (C_{max}, μg/mL), obtained directly from the observed concentration versus time data
- Time to maximum concentration (t_{max}, h), obtained directly from the observed concentration versus time data

- Area under the plasma concentration-time curve from zero to infinity (AUC, µg·h/mL), calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0-t)}+ C_{last}/\lambda_z$. If the extrapolated area (C_{last}/λ_z) is greater than 20% of AUC, then AUC and related parameters will be not reported.

- Area under the plasma concentration-time curve from zero to time of the last quantifiable concentrations ($AUC_{(0-t)}$, 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)

- Apparent terminal elimination rate constant (λ_z, 1/h)

- Half-life associated with the terminal slope ($t_{½\lambda z}$, h), determined as $\ln(2)/\lambda_z$

- Mean residence time (MRT, h)

- Total body clearance of drug from plasma (CL, L/h) (for ceftaroline fosamil and ceftaroline [apparent CL])

- Volume of distribution based on the terminal phase (V_z, L) (for ceftaroline fosamil and ceftaroline [apparent V_z])

- Volume of distribution at steady state (V_{ss}, L) calculated as the product of MRT and CL for nonsteady-state data (for ceftaroline fosamil and ceftaroline [apparent V_{ss}])

- C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,Cmax}$) (adjusted for differences in molecular weights)

- AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,AUC}$) (adjusted for differences in molecular weights)

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.

Individual ratios of Treatment A/Treatment C (or Treatment E/Treatment C, if applicable) will also be calculated for ceftaroline AUC, $AUC_{(0-t)}$, $AUC_{(0-12)}$, and C_{max}.

The following PK parameters will be calculated for diagnostic purposes and will be listed, but not summarized:

- The time interval (λ_z upper and lower) of the log-linear regression to determine $t_{½\lambda z}$

- Number of data points (λ_z, N) included in the log-linear regression analysis

- Goodness-of-fit statistic for calculation of λ_z (Rsq)
- The percent of AUC which is extrapolated to infinity (AUC_{ex}, %)

A minimum of 3 data points and an Rsq value of >0.8 will be used as the criteria for reliable estimation of λ_z.

Due to collection of a blood sample at the end of the infusion, no additional calculation of a concentration at the end of infusion will be performed. The decision to impute a missing end-of-infusion value, or if there is a large time deviation associated with the end-of-infusion sample, will be made on a case-by-case basis per Standard Operating Procedures and Work Instructions. The approach applied in the analyses will be documented in the CSR.

11.3 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 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, volunteers who receive treatment other than the one designated in the randomization schedule will be analyzed by actual treatment and not by randomized treatment.

12.1.2 Analysis of safety population

All volunteers who receive at least 1 dose of randomized IP, ceftaroline fosamil or placebo, and for whom any postdose data are available, will be included in the safety population.

12.1.3 Pharmacokinetics analysis set

The PK analysis set will include all volunteers who receive at least 1 dose of ceftaroline fosamil and have at least 1 measured concentration of any of the 3 analytes in plasma 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 or violations thought to significantly affect the PK of the IP) from all volunteers who received IP.

12.2 Methods of statistical analyses

12.2.1 General principles

Given the exploratory nature, no formal statistical hypothesis testing will be performed in this study. Standard Operating Procedures and Work Instructions will be used as the default methodology if not otherwise specified.

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

Results from both Part A and Part B will included in the clinical study report.

12.2.2 Subject characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum). Categorical variables will be summarized in frequency tables (frequency and proportion). Tabular summaries will be presented for all Part A and Part B volunteers overall.

12.2.3 Safety and tolerability

Continuous variables (clinical chemistry, hematology, and vital signs) will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) by scheduled time point. Categorical variables (AEs and urinalysis) will be summarized in frequency tables (frequency and proportion).

For Part A, systemic AEs will be summarized by the active treatment received in the respective treatment period (ie, ceftaroline fosamil 600 mg in either 50 or 250 mL infusion volumes). Clinical laboratory and vital sign parameters will be summarized by scheduled assessment (Day -1 to follow-up) for all Part A volunteers overall.

For Part B, AEs will be presented by treatment (ie, ceftaroline fosamil 600 mg in 50, 100, or 250 mL infusion volumes, as applicable). Clinical laboratory and vital sign parameters will be summarized by scheduled assessment (Day -1 to follow-up) for all Part B volunteers overall.

SAEs will be collected from the time when informed consent is signed until the follow-up visit. Non-serious AEs will be collected from Day -1 (first admission period) until the follow-up visit. Adverse events that occur before the first dose of IP will be listed and flagged, but will not be included in the tabular summaries of AEs.

Adverse events will be presented by preferred term and system organ class according to MedDRA classification. Listings of SAEs and AEs that led to withdrawal will be presented and the number of volunteers who had any AEs, SAEs, AEs that led to withdrawal, AEs

judged as causally related to IP by the Investigator, and AEs with severe intensity will be summarized.

Electrocardiogram and physical examination findings will be listed only.

12.2.4 Pharmacokinetics

Individual blood sample collection times, derived sampling time deviations, and concentration-time data will be listed. Pharmacokinetic data will be presented by analyte and treatment (Treatment A or E and Treatment C), as appropriate. Rounding conventions will follow Standard Operating Procedures and Work Instructions.

Plasma concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 will be reported to the same precision as the source data. Plasma concentrations will be summarized by nominal time point using descriptive statistics including the population size (N for sample size and n for available data), geometric mean, geometric coefficient of variation (CV%), arithmetic mean, SD, median, minimum, and maximum.

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 maximum value will be reported from the individual data, and the minimum and median will be set to BLQ.
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be reported for SD and CV% and BLQ will be reported for mean, geometric mean, minimum, median, and maximum.
- The number of BLQ values (n below LLOQ) will be reported for each time point.

Plasma PK parameters and ratios will be summarized by analyte and treatment as appropriate using descriptive statistics including: N, n, geometric mean, CV%, arithmetic mean, SD, median, minimum, and maximum.

Individual and summarized concentration-time profiles will be depicted on linear and semi-logarithmic scales by analyte and/or treatment. Plots of geometric mean and individual

values versus treatments will be presented for ceftaroline AUC, $AUC_{(0-t)}$, $AUC_{(0-12)}$, and C_{max}. Additional graphical presentations of data will be presented as deemed appropriate.

12.2.5 Pharmacodynamics (not applicable)

12.2.6 Infusion Site Reactions (Part A Only)

The occurence of ISRs will be listed with VIP score by infusion volume/treatment combination across all assessments.

ISR incidence (number and percent of subjects) will be presented by infusion volume (50, 100, or 250 mL) and treatment (ceftaroline fosamil or placebo) combination. Incidence will also be cross-tabulated as occurrence (yes/no) across for active vs. placebo by infusion volume and treatment.

Placebo 50 mL will be presented separately to placebo 250 mL to allow the active incidence to be contrasted with its corresponding placebo.

12.3 Determination of sample size

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. A sample size of 24 volunteers is considered sufficient to assess if the low-volume infusion produces an increase in the incidence of ISRs (>40%). Therefore, approximately 32 volunteers will be recruited for Part A of this study to ensure the collection of complete data. This sample size is also sufficient to provide adequate safety data in healthy volunteers of the infusion volumes and placebo.

The PK profiles of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 following a single-dose iv administration of 600 mg ceftaroline fosamil (diluted in 250 mL) over 60 minutes have been characterized in previous studies. In Part B of the current study, although the infusion volumes will be different, this same dose and infusion duration will be administered across treatments and no major differences in exposures are expected. Data collected from approximately 8 volunteers is deemed adequate to characterize the PK of the 3 analytes in Treatment A (or Treatment E) and Treatment C.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.5.**

In the case of a medical emergency the Investigator may contact the CPA Physician. If the CPA Physician is not available, contact the CPA Program Director as detailed below.

Name	Role in the study	Address & telephone number

13.2 Overdose

No specific information is available on the treatment of overdosage with ceftaroline fosamil. 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.

13.3 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.

13.3.1 Maternal exposure

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

13.3.2 Paternal exposure

Pregnancy of a volunteer's partner is not considered to be an AE. However, any conception occurring from the date of dosing until 3 months after dosing should be reported to AstraZeneca and followed up for its outcome.

14. LIST OF REFERENCES (NOT APPLICABLE)

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

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

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

ASTRAZENECA SIGNATURE(S)

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

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

SIGNATURE OF PRINCIPAL INVESTIGATOR

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

---

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Centre No.: 1

Appendix B
Additional Safety Information

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

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the 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.

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
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"

Appendix E

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 Amendment

Amendment Number	1
Drug Substance	Ceftaroline fosamil
Study Code	D3720C00015 (P903-30)
Date	
Protocol Dated	

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

For logistical reasons the data for this study will be collected on paper CRFs at instead of the Phase I electronic data capture system. Changes in the CSP from eCRF to CRF have not been documented in this summary.

Section of protocol affected:

Protocol Synopsis (page 2)

Previous text:

Principal Investigator

Revised text:

Principal Investigator

Section of protocol affected:

Table 3 Table of assessments for Part B (page 29)

Previous text:

Alcohol, cotinine, and urine drug screening	X	X

Revised text:

Urine drug screening, alcohol breath test and smokerlyzer test	X	X

Section of protocol affected:

4.2 Exclusion criteria (page 34)

Previous text:

13. Positive screen for drugs of abuse, or cotinine (nicotine) at screening or positive screen for drugs of abuse, alcohol or cotinine on admission to the unit prior to the first administration of IP

Revised text:

13. Positive screen for drugs of abuse, or smokerlyzer test at screening or positive screen for drugs of abuse, alcohol breath test or smokerlyzer test on admission to the unit prior to the first administration of IP

Section of protocol affected:

5.4.1 Methods for ensuring blinding (page 38)

Previous text:

Part A of this study is double-blind with regard to treatment (ceftaroline or placebo). The following personnel will have access to the randomization list:

- The AstraZeneca personnel carrying out the labeling and packaging of IP
- The pharmacy personnel preparing IP at the site

The randomization 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 and tubing will be amber colored to maintain the blind.

Revised text:

Part A of this study is double-blind with regard to treatment (ceftaroline or placebo). The following personnel will have access to the randomization list:

- The AstraZeneca personnel carrying out the labeling and packaging of IP
- The pharmacy personnel preparing and labelling IP at the site

The randomization 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 ~~colored~~ (see handling instructions) to maintain the blind.

Section of protocol affected:

5.5.1 Identity of investigational product(s) (page 39)

Previous text:

The constitution time should be no more than 120 seconds. The constituted and diluted ceftaroline fosamil iv solutions should be administered promptly; however, the constituted vial is stable for up to 4 hours at room temperature. Once the constituted vial is diluted in the infusion bag or bottle, it should be administered within 6 hours of the initial constitution or within 24 hours if the bag or bottle is stored in the refrigerator at 2° to 8°C.

Revised text:

The constitution time should be no more than 120 seconds. After constitution of ceftaroline fosamil vials, infusion solution preparation must be completed within 30 minutes. 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.

Section of protocol affected:

6.2.1 Screening procedures (page 45)

Previous text:

- A urine sample for routine urinalysis (including microscopic examination), drugs of abuse screen, alcohol and cotinine screen

Revised text:

- A urine sample for routine urinalysis (including microscopic examination), drugs of abuse screen
- Alcohol breath test and smokerlyzer test

Section of protocol affected:

6.3.1 Local tolerability measurements (page 46)

Previous text:

For those volunteers who experience an ISR, their washout period may be extended beyond 3 days to allow recovery of the infusion site.

Revised text:

For those volunteers who experience an ISR, their washout period may be extended ~~beyond 3 days~~ to allow recovery of the infusion site.

Section of protocol affected:

6.3.6 Laboratory safety assessment (page 49 and 50)

Previous text:

Additionally, at screening all volunteers will be tested for HIV, HBsAg, and antibodies to HCV. If indicated for females, FSH will be measured to determine their menopausal status at screening. Urine will be tested for alcohol and drugs of abuse at screening and admission to the study center on Day -1 including amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, phencyclidine, tetrahydrocannabinoid, benzodiazepines, and opiates.

Urine will also be screened for cotinine at screening. For female volunteers a serum pregnancy test will be performed at screening and a urine test on each admission to the study center (Day -1).

Revised text:

Additionally, at screening all volunteers will be tested for HIV, HBsAg, and antibodies to HCV. If indicated for females, FSH will be measured to determine their menopausal status at screening. Urine will be tested for drugs of abuse at screening and admission to the study center on Day -1 including amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, phencyclidine, tetrahydrocannabinoid, benzodiazepines, and opiates. For female volunteers a serum pregnancy test will be performed at screening and a urine test on each admission to the study center (Day -1).

Alcohol breath test and smokerlyzer test will be conducted at screening and admission.

Section of protocol affected:

Table 7 Volume of blood to be drawn from each subject (page 52)

Previous text:

			Part A		Part B	
Assessment		**Sample volume (mL)[a]**	**No. of samples**	**Total volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	5	6	30	4	20
	Hematology	2	6	12	4	8
	Serology	3.5	1	3.5	1	3.5
	Serum pregnancy test[b]	3.5	1	3.5	1	3.5
	FSH[b]	3.5	1	3.5	1	3.5
Pharmacokinetic	ceftaroline fosamil, ceftaroline, and ceftaroline M-1	4	0	0	30	120
Total	Males			45.5		151.5
	Females			52.5		158.5

a If a cannula is used, an additional 1 mL of blood will be collected to flush the cannula.
b Female subjects only; FSH will be assessed if indicated to determine volunteer's menopausal status

Revised text:

Assessment		Sample volume (mL)[a]	Part A		Part B	
			No. of samples	Total volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.5	6	15	4	10
	Hematology	2	6	12	4	8
	Serology, serum pregnancy test and FSH	2.5	1	2.5	1	2.5
Pharmacokinetic	ceftaroline fosamil, ceftaroline, and ceftaroline M-1	4	0	0	30	120
Total				29.5		140.5

a If a cannula is used, an additional 1 mL of blood will be collected to flush the cannula.
b Pregnancy test and FSH in female subjects only; FSH will be assessed if indicated to determine volunteer's menopausal status

Section of protocol affected:

10. DATA MANAGEMENT (page 58)

Previous text:

A 21 CFR part 11 compliant electronic data capture (EDC) system will be used for this study. Electronic CRFs will be produced by for each subject. The majority of study data collected will be either directly entered by clinical research staff or directly captured from devices onto the electronic CRF. Data will be available for AstraZeneca review via predefined reports extracted from the database at agreed intervals. The electronic CRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

When direct data entry onto the electronic CRF is inappropriate or impractical data will be collected on paper source documents and subsequently transcribed, where necessary, onto the electronic CRFs by the clinical research staff of . All source documents will be retained by . Photocopies of completed source documents will be provided only if essential (ie, for regulatory purposes) at the request of the AstraZeneca.

Laboratory data are managed within the laboratory information management system and only the date and time of sampling are recorded in the electronic CRF. Data that are not directly captured eg, safety laboratory results and AE coding, are managed externally from the main study database. These data will be merged with the data from the main study database in post-production. Datasets supplied to AstraZeneca will contain all study data.

The informed consent will be kept with a copy of the completed source documents in the appropriate file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

All electronic CRF entries, corrections, and alterations must be made by the Investigator or other, authorised, study-site personnel and only by individuals who have received training on the EDC system. Site staff may be allowed access to the system only after training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained

The Data Management Plan will describe the methods used to collect, check and process clinical data in detail. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process.

Validity and consistency of data will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the course of the study. The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the electronic CRFs are accurate and correct. After completion of the study and when all collected data is validated, the database will be locked. Final data will be extracted from the EDC system and delivered to AstraZeneca in the form of SAS® datasets in accordance with defined project standards. A portable document format (PDF) copy of the electronic CRF will be produced for each study subject and included in the final delivery.

Adverse event and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary.

The EDC system will keep track of all data entry, alterations and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside with the Dictionary coding.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database. External data reconciliation will be done with the clinical database as applicable.

SAE/AE Reconciliation

Serious Adverse Event Reconciliation Reports are produced and reconciled with the Patient Safety database and/or the Investigational Site.

Data verification and validation

The source data verification will be carried out by a site monitor comparing database entered data to source documents (ie, ECG print-outs, laboratory results and other health

records at the study site). Questions and corrections will be noted and verified by the Investigator.

Revised text:

Data management will be performed by

The data in this study will be collected using paper CRFs.

When the completed paper CRF 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

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

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

When all data have been coded, validated and signed the database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca as described in the Laboratory Manual.

Section of protocol affected:

13.1 Medical emergencies and AstraZeneca contacts

Previous text:

Revised text:

_____		_____
	_____ _____	_____

The following information was amended in the protocol as part of the ethics review (revised protocol dated), the changes were classified as non substantial but are included here for completeness

Section of protocol affected:

4.2 Exclusion criteria (page 34)

Previous text:

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

16. For Part B, plasma donation within 1 month of screening or any blood donation, blood product donation, or blood loss greater than 500 mL during the 3 months prior to screening

Revised text:

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

8. Abnormal vital signs, after 10 minutes supine rest, defined as any of the following:

- Systolic blood pressure >140 mm Hg
- Diastolic blood pressure >90 mm Hg

~~16.~~17 For Part B, plasma donation ~~within 1 month of screening~~ or any blood donation, blood product donation, or blood loss greater than 500 mL during the 3 months prior to screening

Section of protocol affected:

5.1 Restrictions during the study (page 36)

Previous text:

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

8 Male volunteers should use a condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm or fathering a child from the date of dosing until 3 months after dosing with the IP. Women of childbearing potential must be using a highly-effective form of birth control for 1 month before enrolment (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.

Revised text:

7. Volunteers participating in Part B of the study should abstain from blood or plasma donation from 3 months before screening until 3 months after ~~final medical examination at the study follow-up~~ screening

8. Male volunteers should use a condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm or fathering a child from the date of dosing until 3 months after dosing with the IP; 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. 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.

Persons who initiated the Amendment:

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

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

---

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review

I agree to the terms of this study protocol/amendment.

ASTRAZENECA SIGNATURE(S)

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

---

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

SIGNATURE OF PRINCIPAL INVESTIGATOR

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

---

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer revie.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Centre No.: 1

AstraZeneca CEREXA

PROTOCOL SYNOPSIS

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

Principal Investigator

Study center(s) and number of subjects planned

This study will be conducted in 2 parts at a single center in the United Kingdom.

Initially, approximately 32 healthy male and female volunteers will be enrolled in Part A to ensure a total of 24 evaluable volunteers (50 mL infusion volume). An additional 32 volunteers may be enrolled to assess a 100-mL infusion volume following review of the 50 mL data. For Part B, 10 healthy male and female volunteers will be enrolled to ensure completion of at least 8 volunteers.

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

Objectives

Primary objective

The primary objective of Part A is to evaluate the local tolerability of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions).

The primary objective of Part B is to characterize the pharmacokinetics of ceftaroline in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes.

Secondary objectives

The secondary objective of Part A is to evaluate the safety of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions).

The secondary objectives of Part B are:

- To characterize the pharmacokinetics of ceftaroline fosamil (the prodrug of ceftaroline) and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes

- To evaluate the safety and tolerability of ceftaroline in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes

Study design

This is a Phase I, single-center, 2-part, randomized study to assess the local tolerability, safety, and pharmacokinetics of ceftaroline in healthy male and female adult volunteers, aged 18 to 75 years, inclusive. Part A will utilitze a placebo-controlled, double-blind, multiple-dose, 2-way crossover design to assess the local tolerability of ceftaroline following multiple infusions of ceftaroline fosamil 600 mg and placebo, each in 50-mL and 250-mL infusion volumes. If the subjects receiving the active 50-mL infusion volume have an incidence of infusion site reactions of >40%, Part A may be repeated using 100-mL and 250-mL infusion volumes. The decision will be made following discussion between the Investigator and the Sponsor and will be based on review of the 50 mL, 250 mL (and corresponding placebo) data. Part B will be conducted following Part A and will utilize an open-label, single-dose, 2-way crossover design to evaluate the pharmacokinetics of ceftaroline in either 50-mL and 250-mL infusion volumes or 100-mL and 250-mL infusion volumes, depending on the safety and local tolerability results from Part A.

Part A (Assessment of local tolerability)

Part A of the study is a randomized, placebo-controlled, double-blinded, and 2-way crossover design. Infusion volumes of 50 mL and 250 mL will be studied to facilitate the identification of effects related to the administration of drug diluted in various infusion volumes rather than the study procedures or situations. Initially, 32 volunteers will be enrolled to ensure a total of 24 evaluable volunteers. An additional 32 volunteers may be recruited and dosed to compare a 100 mL infusion volume against the 250-mL infusion volume.

Investigational product will be administered as simultaneous, bilateral (placebo in one arm and active in the other), 60-minute infusions every 12 hours over 72 hours (6 infusions) followed by a minimum 4.5-day (approximately 108 hours) washout and another simultaneous, bilateral, 60-minute infusion (in different veins than used previously) every

12 hours over 72 hours (6 infusions). The following treatments will be administered in Part A:

- Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume
- Treatment B: placebo in 50 mL infusion volume
- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume
- Treatment D: placebo in 250 mL infusion volume

On Day 1, volunteers will be randomly assigned in a 1:1 fashion to 1 of 2 treatment sequences of various infusion volumes of ceftaroline fosamil 600 mg and placebo as outlined below:

Sequence	Crossover period	Left arm	Right arm
Sequence 1	1	50 mL active (Treatment A)	250 mL placebo (Treatment D)
	2	50 mL placebo (Treatment B)	250 mL active (Treatment C)
Sequence 2	1	250 mL active (Treatment C)	50 mL placebo (Treatment B)
	2	250 mL placebo (Treatment D)	50 mL active (Treatment A)

These sequences will avoid administering active treatment in the same arm for both treatment periods and will also avoid administering the same volume to both arms within the same treatment period.

If the 50 mL subjects have an incidence of infusion site reactions of >40%, Part A may be repeated, replacing the 50 mL treatments A and B respectively with:

- Treatment E: 600 mg ceftaroline fosamil in 100 mL infusion volume
- Treatment F: placebo in 100 mL infusion volume

The corresponding treatment sequences will be as shown below:

Sequence	Crossover period	Left arm	Right arm
Sequence 3	1	100 mL active (Treatment E)	250 mL placebo (Treatment D)
	2	100 mL placebo (Treatment F)	250 mL active (Treatment C)
Sequence 4	1	250 mL active (Treatment C)	100 mL placebo (Treatment F)
	2	250 mL placebo (Treatment D)	100 mL active (Treatment E)

The study will be comprised of a screening period of up to 28 days, 2 residential periods of approximately 5 days, separated by a washout period of at least 4.5 days (approximately 108 hours), and a follow-up visit 5 to 10 days after discharge from the unit.

Throughout the residential periods, there will be assessment of local tolerability at the infusion site and safety monitoring (including physical examinations, laboratory assessments, 12-lead electrocardiograms, and vital sign measurements). Local tolerability will be assessed over time. Any local reaction with a visual infusion phlebitis score of 2 or greater (see Appendix D) will be determined as an infusion site reaction and will be recorded as an adverse event. Any infusion site reactions unresolved by the follow-up visit will continue to be monitored for as long as the Investigator considers necessary.

Part B (Assessment of pharmacokinetics)

Part B will be conducted following a review of the local tolerability and safety results from Part A. The doses to be used in Part B of the study will be determined following review of the Part A data. If the volunteers receiving the active 600 mg diluted in 50 mL have an ISR ≤40% during Part A, then Part B will include single doses of the following:

- Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume
- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)

Depending on the results from Part A, the alternative single doses of treatment shown below may be administered in Part B:

- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)
- Treatment E: 600 mg ceftaroline fosamil in 100 mL infusion volume

If neither the 50 mL or 100 mL infusion volumes are tolerated then Part B will not be performed.

Volunteers who are randomized in Part A will not be allowed to enroll in Part B. Part B of the study will consist of a screening period of up to 28 days, a 5-day/4-night residential period, and a follow-up period of 5 to 10 days after discharge from the unit. After the screening period, volunteers who qualify will be asked to return for admission to the study center on Day -1 and will remain confined until discharge. On Day 1, volunteers will be randomly assigned in a 1:1 fashion to either treatment sequence CA or AC (or sequence CE or EC if applicable). The arm infused will switch from the first period to the second and thus the randomization will be stratified by the ordering of infusion (Right-Left and Left-Right), to balance any potential arm effects, and to avoid confounding arm with period effects. A single dose of 600 mg ceftaroline fosamil from the appropriate treatment will be administered intravenously over 60 minutes on Day 1. Following a 1-day washout (Day 2), a single dose of 600 mg ceftaroline fosamil from the appropriate treatment will be administered intravenously over 60 minutes on Day 3. Volunteers will be discharged from the unit on Day 4 after

collection of the 24-hour pharmacokinetic sample in Period 2 and completion of all scheduled assessments.

Plasma pharmacokinetic sample collection and safety assessments including physical examinations, laboratory assessments, 12-lead electrocardiograms, and vital sign measurements will be performed.

Target subject population

Healthy male and female volunteers between the ages of 18 to 75 years, inclusive, will be eligible for study participation. Women of childbearing potential must have a negative pregnancy test (at screening and at each admission), be nonlactating, and be using a highly-effective form of birth control for 3 months before enrollment.

Initially, up to 32 volunteers will be enrolled in Part A to ensure a total of 24 evaluable volunteers (50 mL). An additional 32 volunteers may be enrolled to assess the 100-mL infusion volume. Ten volunteers will be enrolled in Part B in order to have 8 evaluable volunteers.

Investigational product, dosage and mode of administration

Ceftaroline fosamil for infusion will be supplied as 600 mg ceftaroline fosamil dry mixture in a clear glass vial. Vials will be reconstituted and diluted in 0.9% sodium chloride infusion fluid to volumes of 50, 100, or 250 mL, as appropriate. For Part A, investigational product will be administered as 60-minute, intravenous infusions every 12 hours for 72 hours (6 infusions) in each of 2 treatment periods. For Part B, a single infusion of 600 mg ceftaroline fosamil over 60 minutes will be administered in each of 2 treatment periods.

Comparator, dosage and mode of administration

Placebo for Part A will consist of 0.9% sodium chloride infusion fluid of various volumes (ie, 50, 100, or 250 mL), as appropriate. Placebo will be administered as simultaneous, 60-minute, intravenous infusions in the opposite arm from the ceftaroline fosamil infusion.

Duration of treatment

For Part A, the duration of each volunteer's participation will be up to approximately 50 days, including a screening period of up to 28 days, two residential periods of approximately 5 days each separated by a washout of at least 4.5 days (≥108 hours between treatments), and a follow-up visit 5 to 10 days following discharge from the final period. The duration of each volunteer's participation in Part B will be up to 43 days including a 28-day screening period, a 5-day residential period, and a follow-up visit 5 to 10 days following clinic discharge.

For both study parts, volunteers will begin the residential stay on Day -1 (of each period in Part A) and will be discharged after completion of all intravenous infusions, all study-related evaluations, and at the discretion of the Investigator.

Outcome variable(s):

- Safety

  adverse events, including local infusion site tolerability, vital signs, electrocardiograms, clinical laboratory variables, and physical examinations

- Pharmacokinetics (Part B only)

  The following plasma parameters will be calculated, where estimable, for ceftaroline, ceftaroline fosamil, and ceftaroline M-1: maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), area under the 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 [$AUC_{(0-12)}$], apparent terminal elimination rate constant (λ_z), half-life associated with the terminal slope ($t_{½\lambda z}$), mean residence time (MRT), total body clearance of drug from plasma (CL, for ceftaroline fosamil and ceftaroline [apparent CL]), volume of distribution based on the terminal phase (V_z, for ceftaroline fosamil and ceftaroline [apparent V_z]), volume of distribution at steady state (V_{ss}, for ceftaroline fosamil and ceftaroline [apparent V_{ss}]), C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,Cmax}$), and AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,AUC}$)

Statistical methods

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. For Part A, a sample size of 24 volunteers is considered sufficient to assess if the low-volume infusion produces an increase in the incidence of infusion site reactions (incidence >40% in subjects on active treatment). Therefore, approximately 32 volunteers will be recruited for Part A for a given treatment comparison (ie, 50 versus 250 mL or 100 versus 250 mL infusion volumes) to ensure the collection of complete data. This sample size is also sufficient to provide adequate safety data in healthy volunteers of the infusion volumes and placebo.

The pharmacokinetic profiles of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 following a single-dose intravenous administration of 600 mg ceftaroline fosamil (diluted in 250 mL) over 60 minutes have been characterized in previous studies. Although the infusion volumes will be different in Part B of the current study, this same dose and infusion duration will be administered across treatments and no major differences in exposures are expected. Data collected from approximately 8 volunteers is deemed adequate to characterize the pharmacokinetics of the 3 analytes in Treatment A (or Treatment E) and Treatment C.

No formal statistical hypothesis testing will be performed in either part of the study. The safety, tolerability, and pharmacokinetic data will be summarized using descriptive statistics, frequency counts, or graphically, as appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol (CSP).

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.2)
AUC	Area under the concentration-time curve from zero to infinity
$AUC_{(0-t)}$	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
$AUC_{ex\%}$	Percent of AUC extrapolated
B	Blood
BCRP	Breast cancer resistance protein
BLQ	Below the lower limit of quantification
BMI	Body mass index
CABP	Community-acquired bacterial pneumonia
CAP	Community acquired pneumonia
CL	Total body clearance of drug from plasma
C_{max}	Maximum plasma concentration
CPA	Clinical Pharmacology Alliance
C_rCL	Creatinine clearance
CRF	Case report form
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
cSSSI	Complicated skin and skin structure infections
cSSTI	Complicated skin and soft tissue infections
CV%	Geometric coefficient of variation
CYP450	Cytochrome P450
ECG	Electrocardiogram
EDC	Electronic data capture
ESRD	End-stage renal disease

Abbreviation or special term	Explanation
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
ICH	International Conference on Harmonization
IP	Investigational product
ISR	Infusion site reaction
iv	Intravenous
λ_z	Apparent terminal elimination rate constant
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NA	Not applicable
ND	Not determined
NDA	New Drug Application
OAE	Other Significant Adverse Event (see definition in Section 11.1.2)
OAT	Organic anion transporter
P-gp	P-glycoprotein
PK	Pharmacokinetics
$R_{M/D,Cmax}$	C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline
$R_{M/D,AUC}$	AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline
Rsq	Goodness-of-fit statistic
S	Serum
SAE	Serious adverse event (see definition in Section 6.3.3).
SD	Standard deviation
$t_{½\lambda z}$	Half-life associated with the terminal slope

Abbreviation or special term	Explanation
t_{max}	Time to maximum concentration
U	Urine
US	United States
V_z	Volume of distribution based on the terminal phase
V_{ss}	Volume of distribution at steady state
VIP	Visual Infusion Phlebitis

1. INTRODUCTION

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

1.1 Background

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, which carry out the final steps in cell wall biosynthesis.

The safety pharmacology program assessed the central nervous system, 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 program. In vitro human ether-à-go-go-related gene and dog Purkinje fibers 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, convulsions or proconvulsive behavior has not been seen in subjects.

Nonclinical absorption, distribution, metabolism, and excretion studies did not raise any significant issues that adversely impacted on the development of ceftaroline fosamil. Ceftaroline fosamil and/or metabolites were rapidly distributed throughout the body following single doses of radiolabelled ceftaroline fosamil to 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 dosing of [^{14}C] ceftaroline fosamil of 14 days in rats, the highest concentration of radioactivity was detected in the kidney followed by the skin. Radioactivity concentrations in other tissues were lower than those observed in plasma.

Following a single intravenous (iv) dose of [^{14}C] ceftaroline fosamil to rats and monkeys, the dose was excreted in urine predominantly as ceftaroline and its open-ring metabolite, ceftaroline M-1. Only a very small amount (less than 1%) of ceftaroline fosamil was excreted in the urine of monkeys, while 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 tested. 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.

The nonclinical safety program assessed the toxicity of ceftaroline fosamil and the active component, ceftaroline, in the rat and monkey administered for up to 3 months. The primary toxicities observed were renal toxicity, convulsions, and reactions at the injection site. These findings are also commonly observed both preclinically and clinically with other iv administered cephalosporins. Changes in the kidney included collecting duct hypertrophy or vacuolation, deposition of foreign material associated with granuloma formation, and associated pyelitis. The renal changes tended to recover following 4-week nondosing periods in the rat and monkey and, furthermore, there was no obvious compromise of kidney function. There was some evidence of inflammation at the injection site in repeated-dose studies in rats but not in monkeys. It is noteworthy that the clinical preparation contains L-arginine, which is a known irritant. However, in rabbit studies using this preparation, venous or muscular irritation was not a major concern. Furthermore, although injection site reactions are present at a low level, clinical studies have not had a significant issue with local irritation.

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

The clinical development program for ceftaroline fosamil is comprised of 17 clinical studies, including 2 Phase III cSSSI and 2 Phase III CABP safety and efficacy clinical studies. Approximately 1700 subjects have received ceftaroline as a part of this program. At the recommended dosing regimen of 600 mg ceftaroline fosamil administered as a 60-minute iv infusion every 12 hours for 5 to 14 days for treatment of cSSSI and 5 to 7 days for treatment of CABP, ceftaroline fosamil was well tolerated and demonstrated a favorable safety profile that was compatible with treatment of cSSSI and CABP and known cephalosporin class effects.

The FDA has agreed to a reduced dosage adjustment in patients with moderate (creatinine clearance [CrCL] of greater than 30 to 50 mL/min or less) or severe (CrCL of 15 mL/min or more to 30 mL/min or less) renal impairment and in patients with ESRD (CrCL less than 15 mL/min) as calculated using the Cockcroft-Gault formula. These dose adjustments are as follows:

- Moderate renal impairment: 400 mg ceftaroline fosamil infused over 1 hour every 12 hours
- Severe renal impairment: 300 mg ceftaroline fosamil infused over 1 hour
- End-stage renal disease: 200 mg ceftaroline fosamil infused over 1 hour

The incidences of adverse events (AEs) experienced by subjects receiving ceftaroline fosamil were similar compared with those experienced by subjects receiving comparator therapies. The majority of the AEs experienced were mild or moderate in severity and were assessed as unrelated to ceftaroline fosamil administration. Furthermore, the incidences of death, serious AEs (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 reveal that potential adverse cardiac, renal, or hepatic effects observed 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 seroconversion from a negative to a positive direct Coombs' test were higher in the ceftaroline group compared with the comparator groups, no subject was identified with clinical findings or laboratory results that were consistent with hemolytic anaemia. The incidence of potential antibiotic-associated diarrhea (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 study drug or from the study due to AEs of diarrhea in both treatment groups. Confirmed cases of *Clostridium difficile*-associated diarrhea were rare in both treatment groups.

At the clinical dosages of ceftaroline fosamil studied (600 mg iv every 12 hours or 400 mg iv every 12 hours given as 60-minute infusions), ceftaroline demonstrated an acceptable safety profile that was compatible with treatment of cSSSI and CABP. In addition, no safety concerns were identified in the safety review beyond those already known to be cephalosporin class effects.

The cumulative clinical experience with ceftaroline identified the following adverse reactions:

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, anemia
Nervous system disorders	Headache, dizziness
Gastrointestinal disorders	Diarrhea, nausea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria
Vascular disorders	Phlebitis
Immune system disorders	Hypersensitivity or anaphylaxis
Infections and infestations	*Clostridium difficile* colitis
Investigations	Increased blood creatinine and transaminases, prolonged prothrombin time, international normalized ratio increased, positive direct Coombs
General disorders and administrative site conditions	Infusion site reactions, erythema, pain, phlebitis, pyrexia

This information appears in Table 10-1 of the Investigator Brochure.

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

- Rapid conversion of the prodrug, ceftaroline fosamil, by phosphatases to active ceftaroline in plasma
- Low human plasma protein binding (approximately 20%) of ceftaroline with no distribution into erythrocytes
- Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve increase approximately proportionally to dose (50 to 1000 mg), with a terminal half-life ($t_{1/2}$) of 2 to 3 hours
- Metabolized by opening of ceftaroline's β-lactam ring to ceftaroline, the microbiologically inactive metabolite M-1, and additional minor unidentified metabolites
- No inhibition or induction of cytochrome P450 (CYP450) isoenzymes in vitro
- No metabolism by CYP450 isoenzymes in vitro
- No accumulation or time-dependent PK observed after repeated doses every 12 hours

- Eliminated mainly through renal excretion (clearance is approximately equivalent to the glomerular filtration rate)
- Ceftaroline is not a substrate or inhibitor of human active renal uptake transporters, organic cation transporter-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 fecal intestinal flora
- No dose adjustment needed based on gender, age, or mild renal impairment

For further information, please refer to the Investigator Brochure.

The Sponsor will immediately notify the Principal Investigator if any relevant new safety or toxicology information becomes available during the study.

1.2 Rationale for conducting this study

Part A of this study will evaluate the local tolerability of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted into various infusion volumes (50 mL and 250 mL or 100 mL) and infused every 12 hours into the same vein over 60 minutes, for a maximum of 72 hours (6 infusions). The results from this part of the study will provide clinical data on the tolerability using infusion volumes lower than the 250 mL previously studied in clinical trials.

Part B of the study will be conducted to characterize the single-dose PK of ceftaroline, its prodrug (ceftaroline fosamil), and metabolite (ceftaroline M-1) at the same infusion regimens/volumes as the active treatments in Part A (600 mg ceftaroline diluted in volumes of 50 mL [or 100-mL] and 250 mL). As the dose and infusion duration will remain the same in all treatments, the exposure profiles are expected to be similar across treatments.

1.3 Benefit/risk and ethical assessment

This study will not provide any direct medical benefits to volunteers who participate. The major risk for volunteers who participate in the study is from AEs induced by ceftaroline and the risks associated with iv access.

The potential AEs that may occur with the use of ceftaroline in humans should be evaluated in the context of known cephalosporin-class AEs. Typical class effects include hypersensitivity and allergic reactions, nausea, diarrhea including *C. difficile* colitis, skin rash, leukopenia, thrombocytopenia, eosinophilia, positive Coombs' test, abnormal coagulation, and elevation

of hepatic enzymes. These effects are generally transient and spontaneously reversible after administration of the cephalosporin has been stopped. Severe reactions to cephalosporins including seizures, nephrotoxicity, hemolytic anemia, severe cutaneous reactions, anaphylaxis, and death are infrequent.

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

The incidence of subjects with infusion site reactions during the Phase III studies (cSSSI and CAP combined) was 2.2% for Ceftaroline and 1.6% for comparators. The following infusion site reactions were reported at an incidence up to 0.5% each during ceftaroline treatment: erythema, pain, phlebitis, extravasation, swelling, pruritus and thrombosis.

In a healthy volunteer Phase I study (study P903-01), ceftaroline fosamil was administered in single doses of up to 1000 mg and multiple doses of up to 800 mg. These were given in volumes of 140 mL and infused over 60 minutes. Adverse events related to the injection site (injection site pain/discomfort/thrombophlebitis) were seen in 44% of volunteers who were on active drug. The events were mild in severity. In another healthy volunteer Phase I study (study P903-20), ceftaroline fosamil was administered in single doses of up to 2000 mg and multiple doses of up to 600 mg. These were given in volumes of 250 mL and infused over 60 minutes. One of 16 volunteers on the single dose and 2 of 8 volunteers on the multiple dose had a mild AE related to the infusion site.

Monitoring will be performed according to Good Clinical Practice (GCP) and guidelines of the International Conference on Harmonization (ICH). Additionally, the AEs of hemolytic anemia, acute renal failure, seizure/convulsions, and drug-induced liver injury are currently classified as important potential risks for ceftaroline in the global and EU Patient Risk Management Plan. If 1 of these 4 aforementioned AEs occurs, irrespective of seriousness, the AstraZeneca Patient Safety Physician should be contacted in a timely manner to ensure appropriate data collection for proper safety evaluation.

Clinical laboratory, electrocardiogram (ECG), and vital sign results for volunteers in this study will be monitored and clinically significant abnormalities will be reviewed and assessed by the Investigator. Infusion site reactions (ISRs) will be monitored closely and volunteers who experience infusion site phlebitis will have their infusions discontinued.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of Part A of the study is to evaluate the local tolerability of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions).

The primary objective of Part B is to characterize the PK of ceftaroline in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes.

2.2 Secondary objectives

The secondary objective of Part A of the study is to evaluate the safety of ceftaroline in healthy volunteers when ceftaroline fosamil 600 mg is diluted in various infusion volumes and infused into the same vein over 60 minutes every 12 hours for 72 hours (6 infusions).

The secondary objectives of Part B are:

- To characterize the PK of ceftaroline fosamil (the prodrug of ceftaroline) and ceftaroline M-1 (the microbiologically inactive metabolite of ceftaroline) in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes

- To evaluate the safety and tolerability of ceftaroline in healthy volunteers following a single-dose administration of ceftaroline fosamil 600 mg diluted in various infusion volumes and infused over 60 minutes

3. STUDY PLAN AND PROCEDURES

This CSP has been subject to a peer review according to AstraZeneca standard procedures.

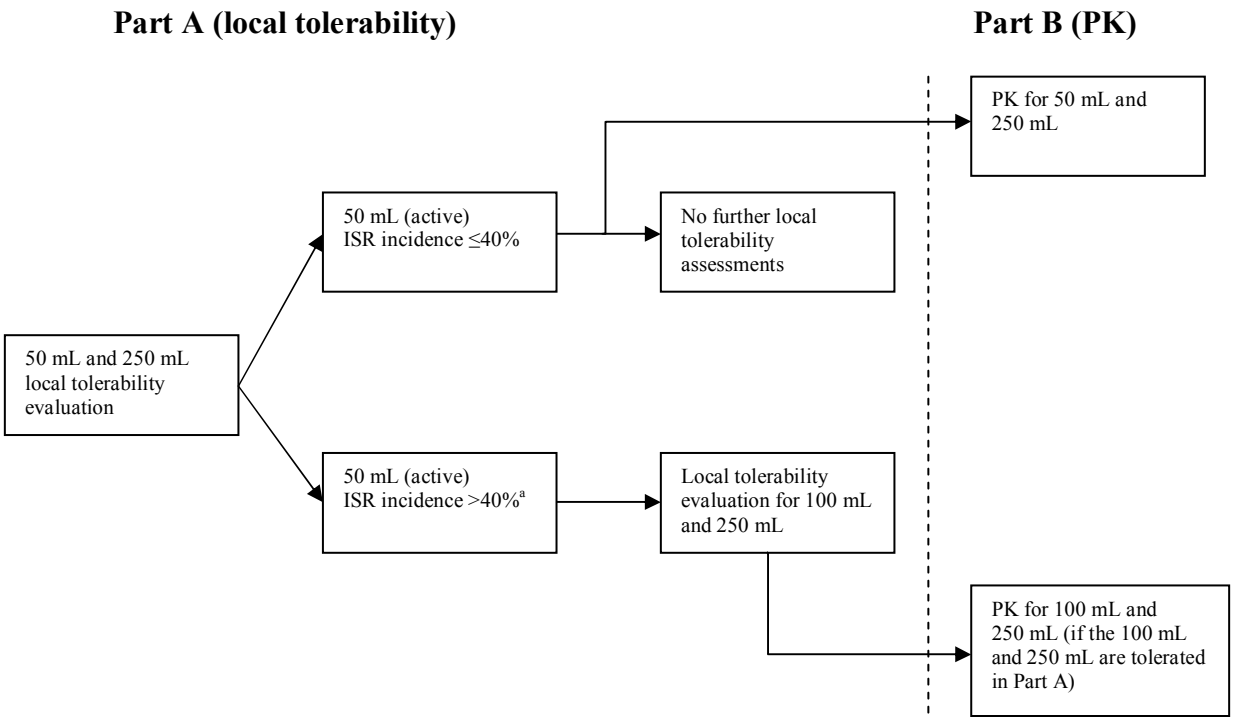
3.1 Overall study design and flow chart

This is a Phase I, single-center, 2-part, randomized study to assess the local tolerability, safety, and PK of ceftaroline in healthy male and female adult volunteers, aged 18 to 75 years, inclusive. Part A will utilitze a placebo-controlled, double-blind, multiple-dose, 2-way crossover design to assess the local tolerability of ceftaroline following multiple infusions of ceftaroline fosamil 600 mg and placebo, each in 50-mL and 250-mL infusion volumes. If the subjects receiving the active 50-mL infusion volume have an incidence of infusion site reactions of >40%, Part A may be repeated using 100-mL and 250-mL infusion volumes. The decision will be made following discussion between the Investigator and the Sponsor and will be based on review of the 50 mL, 250 mL (and corresponding placebo) data (see Section 5.8 for details). Part B will be conducted following Part A and will utilize an open-label, single-dose, 2-way crossover design to evaluate the PK of ceftaroline in either 50-mL and 250-mL

infusion volumes or 100-mL and 250-mL infusion volumes, depending on the local tolerability results from Part A.

A flow chart for the overall study design is presented in Figure 1.

Figure 1 Overall study flow chart



ISR = Infusion site reaction (ie local reaction with a visual infusion phlebitis score of 2 or greater)
For detailed procedures in data review and stopping criteria, see Section 5.8.
a Whether 100 mL investigation is progressed will be based on a review of the 50 mL data compared to the 250 mL and corresponding placebo arms and discussion between Sponsor and Investigator.

3.1.1 Part A

Part A of the study is randomized, placebo-controlled, double-blinded, and a 2-way crossover design to minimize bias. Infusion volumes of 50 mL and 250 mL will be studied to facilitate the identification of effects related to the administration of drug diluted in various infusion volumes rather than the study procedures or situations. Initially, 32 volunteers will be enrolled to ensure at least 24 evaluable volunteers. An additional 32 volunteers may be recruited and dosed to compare a 100-mL infusion volume against the 250-mL infusion volume, based on the incidence of ISRs following the 50-mL infusion.

Tolerability will be deterimined by clinical evaluation of the subjects. Detailed procedures for data review and stopping criteria are described in Section 5.8. If the incidence of ISRs in the

active 50 mL subjects is deemed acceptable (≤40%), then the comparison of the 100-mL infusion volume will not be made to the 250-mL standard (reference) volume. If the 50-mL infusion volume study results indicate the incidence of ISRs is >40%, as detailed in Section 5.8, then the study may be repeated with a comparison of a 100-mL infusion against the 250-mL standard (reference) volume.

Investigational product (IP) will be administered as simultaneous, bilateral, 60-minute infusions every 12 hours over 72 hours (6 infusions) followed by a washout of at least 4.5 days (approximately 108 hours) and another simultaneous, bilateral, 60-minute infusion (in different veins than used previously) every 12 hours over 72 hours (6 infusions). The following treatments will be administered in Part A:

- Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume
- Treatment B: placebo in 50 mL infusion volume
- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume
- Treatment D: placebo in 250 mL infusion volume

On Day 1, volunteers will be randomly assigned in a 1:1 fashion to 1 of 2 treatment sequences of various infusion volumes of ceftaroline fosamil 600 mg and placebo as detailed in Section 5.2. These sequences will avoid administering active treatment in the same arm for both treatment periods and will also avoid administering the same volume to both arms within the same treatment period.

If the active 50-mL infusion subjects have an incidence of ISRs of >40%, the following treatments may be administered (see Section 5.8):

- Treatment E: 600 mg ceftaroline fosamil in 100 mL infusion volume
- Treatment F: placebo in 100 mL infusion volume

This part of the study consists of a 28-day maximum screening period, followed by 2 residential periods of 5 days each separated by a washout of at least 4.5 days (approximately 108 hours), and concludes with a follow-up visit 5 to 10 days after the volunteer is discharged from the final period.

Volunteers will undergo screening assessments during the 28-day period preceding administration of the first infusion of IP. The study assessments and their timings for Part A are outlined in Table 2. Volunteers who meet eligibility criteria will be asked to return to the unit the day before the administration of the first infusion of IP (Day -1) and additional assessments will be performed to ensure they continue to meet the eligibility criteria before beginning each residential period.

For the first infusion of each period, local tolerability will be assessed at predose and at 20, 40, and 60 minutes, 6 hours, and 12 hours after the start of the infusion; the 12-hour assessment will be conducted prior to start of the second infusion. For the subsequent second to sixth infusions, local tolerability will be assessed at 20, 40, and 60 minutes, 6 hours, and 12 hours after the start of the infusion; the 12-hour assessment will be conducted prior to the start of the following infusion.

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. Safety assessments including physical examinations, laboratory assessments, 12-lead ECGs, and vital sign measurements will be performed according to the schedule in Table 2. The study flow chart for Part A is shown below in Figure 2.

Figure 2 Study flow chart for Part A

Visit 1[a] Screening	Visit 2 (Residential period 1)			Visit 3 (Residential period 2)		Visit 4 Follow-up
	Admission	simultaneous bilateral infusions	Washout	Admission	simultaneous bilateral infusions	
	Confirm eligibility and baseline assessments; enroll up to 32 healthy volunteers (24 to complete)	Dosing every 12 hours (6 infusions) on Days 1-3, discharge on Day 4		Confirm eligibility and baseline assessments	Dosing every 12 hours (6 infusions) on Days 1-3, discharge on Day 4	
≤28 days	Day -1	Days 1-4	≥4.5 days[b]	Day -1	Days 1 to 4	5-10 days after final discharge

a Visit 1 may be conducted over 1 or more days during the screening period.
b A minimum washout between treatments of at least 4.5 days (approximately 108 hours). The washout period may be extended if required for resolution of any ISRs experienced by a volunteer in the first treatment period.

Table 2 Table of assessments for Part A

Visit	1	2 and 3 (Residential periods 1 and 2[a])				4
Assessments	**Screening**	**Admission**	**Simultaneous bilateral infusions**			**Discharge[b]**	**Follow-up**
Days	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**(5-10 days after final discharge)**
Informed consent[c]	**X**						
Inclusion/exclusion criteria	X	X					
Demography	X						
Medical/surgical and smoking history	X						
Prior/concomitant medication	X	X	X	X	X	X	X
Complete physical examination	X	X				X	
Supine blood pressure and pulse[d]	X	X	X	X	X	X	X
Height/weight and BMI calculation[e]	X					X	X
12-Lead ECG[f]	X	X				X	
Clinical chemistry/hematology/ urinalysis[g]	X	X				X	X
Viral serology	X						
Estimate creatinine clearance[h]	X					X	
Urine drug screening, alcohol breath test and smokerlyzer test	X	X					
Serum/urine pregnancy test[i]	X	X					
FSH[j]	X						
Randomization[k]			X				
Administer dose[l]			X	X	X		
Vascular access site assessments[m]			X	X	X	X	
Record AEs/SAEs[n]	X	X	X	X	X	X	X

AE adverse event; BMI body mass index; ECG electrocardiogram; FSH follicle-stimulating hormone; SAE serious adverse event.

a Volunteers will be admitted for 2 indentical treatment periods. Period 1 and 2 will be separated by a minimum washout period of 4.5 days (approximately 108 hours) between treatments. The washout may be extended at the discretion of the Investigator) if required for resolution of any ISRs experienced by a subject in the first treatment period.

b Volunteers will be discharged on Day 4 following completion of assessments.

c Informed consent will be collected prior to any procedures being performed.
d Supine blood pressure and pulse will be evaluated after the volunteer has rested in the supine position for at least 10 minutes prior to the evaluation. If possible, the same arm and equipment should be used for each evaluation. On Days 1 to 3, blood pressure and pulse will be evaluated in the morning prior to infusion.
e Height/weight will be evaluated and BMI calculated at the screening visit. Only weight will be evaluated upon discharge and follow-up
f A 12-lead ECG will be performed after the volunteer has rested in the supine position for 10 minutes prior to the evaluation.
g The volunteer will fast for at least 4 hours prior to clinical laboratory evaluations.
h Creatinine clearance will be estimated using the Cockcroft-Gault formula at screening and discharge.
i A serum pregnancy test will be performed at screening and a urine pregnancy test at all other time points for all women of childbearing potential. If positive, the volunteer is excluded from participation in the study.
j Performed as appropriate to confirm postmenopausal status.
k Volunteers will be randomized in the morning of Day 1, Period 1, just prior to IP administration.
l Crossover periods: The duration of dosing will start at the initial drug infusion and will continue every 12 hours until the volunteer has received multiple infusions up to 72 hours for a total of 6 infusions during each crossover period. Volunteers who experience a Visual Infusion Phlebitis score of 2 or more will not have any further infusions in the affected arm for the treatment period. The infusion in the contralateral arm may continue if the infusion site is healthy.
m Vascular access site review of local tolerability will be performed by viewing in good lighting each of the infusion sites predose and at 20, 40, and 60 minutes, 6 hours, and 12 hours after the start of the infusion; the 12-hour assessment will be conducted prior to start of the second infusion. For the subsequent second to sixth infusions, local tolerability will be assessed at 20, 40, and 60 minutes, 6 hours, and 12 hours after the start of the infusion; the 12-hour assessment will be conducted prior to the start of the following infusion. Assessment will also occur as clinically indicated. A local reaction will be determined as an ISR and will be recorded as an AE when the severity score is 2 or more as measured by the Visual Infusion Phlebitis scale included in Appendix D.
n SAEs will be collected from the time when informed consent is signed until the follow-up visit. Non-serious AEs will be collected from Day -1 of Period 1 until the follow-up visit.

3.1.2 Part B

Part B will be conducted following a review of the local tolerability and safety results from Part A. The doses to be used in Part B of the study will be determined following review of the Part A data. If the volunteers receiving the active 600 mg diluted in 50 mL have an ISR ≤40% during Part A, then Part B will include single doses of the following:

- Treatment A: 600 mg ceftaroline fosamil in 50 mL infusion volume
- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)

Depending on the results from Part A, the alternative single doses of treatment shown below may be administered in Part B (see Section 5.8):

- Treatment C: 600 mg ceftaroline fosamil in 250 mL infusion volume (reference)
- Treatment E: 600 mg ceftaroline fosamil in 100 mL infusion volume

A total of 10 volunteers will be enrolled into Part B in order to have 8 evaluable volunteers. Volunteers who are randomized in Part A will not be allowed to enroll in Part B. Part B of the study will consist of a screening period of up to 28 days, a 5-day/4-night residential period, and a follow-up period of 5 to 10 days after discharge from the unit. After the screening period, volunteers who qualify will be asked to return for admission to the study center on Day -1 and will remain confined until discharge. On Day 1, volunteers will be randomly assigned in a 1:1 fashion to either treatment sequence CA or AC (or sequence CE or EC if applicable). The arm infused will switch from the first period to the second and thus the randomization will be stratified by the ordering of infusion (Right-Left and Left-Right), to balance any potential arm effects, and to avoid confounding arm with period effects. A single dose of 600 mg ceftaroline fosamil from the appropriate treatment will be administered intravenously over 60 minutes on Day 1. Following a 1-day washout (Day 2), a single dose of 600 mg ceftaroline fosamil from the appropriate treatment will be administered intravenously over 60 minutes on Day 3. Volunteers will be discharged from the unit on day 4 after collection of the 24-hour PK sample and completion of all scheduled assessments.

Plasma PK sample collection and safety assessments including physical examinations, laboratory assessments, 12-lead ECGs, and vital sign measurements will be performed according to the schedule in Table 3. The study flow chart for Part B is shown below in Figure 3.

Figure 3 Study flow chart for Part B

Visit 1[a]	Visit 2					Visit 3
Screening	Residential period					Follow-up
	Admission	Crossover Period 1	Washout	Crossover Period 2	Discharge	
	Confirm eligibility; 10 volunteers to be enrolled	Single-dose administration		Single-dose administration	End of clinic safety assessments	
≤28 days	Day -1	Day 1	Day 2	Day 3	Day 4	5-10 days after clinic discharge

[a] Visit 1 may be conducted over 1 or more days during the screening period.

Table 3 Table of assessments for Part B

Visit	1	2 (Residential)					3
Assessments	**Screening**	**Check-in**	**Crossover period 1**	**Washout**	**Crossover period 2**	**Discharge[a]**	**Follow-up**
Days	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**(5-10 days after discharge)**
Informed consent[b]	**X**						
Inclusion/exclusion criteria	X	X					
Demography	X						
Medical/surgical and smoking history	X						
Prior/concomitant medication	X	X	X	X	X	X	X
Complete physical examination[c]	X	X				X	
Brief physical examination[d]				X			
Supine blood pressure and pulse[e]	X	X	X	X	X	X	X
Height/weight and BMI calculation[f]	X						X
12-Lead ECG[g]	X	X				X	
Clinical Chemistry/hematology/urinalysis[h]	X	X				X	X
Viral serology	X						
Estimate creatinine clearance[i]	X					X	
Urine drug screening, alcohol breath test and somokelyzer test	X	X					
Pregnancy test[j]	X	X					
FSH[k]	X						
Randomization[l]			X				
Administer dose[m]			X		X		
Pharmacokinetic samples[n]			X	X	X	X	
Record AEs/SAEs[o]	X	X	X	X	X	X	X

AE adverse event; BMI body mass index; ECG electrocardiogram; FSH follicle-stimulating hormone; SAE serious adverse event.

a Volunteers will be discharged on Day 4 after completion of assessments

b Informed consent will be collected prior to any procedures being performed.

c A complete physical examination will be performed at screening, Day -1, and discharge and includes an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

d A brief physical examination will be performed on Day 2 and includes an assessment of the general appearance, abdomen, lungs, and the cardiovascular systems.
e Supine blood pressure and pulse will be evaluated after the volunteer has rested in the supine position for at least 10 minutes prior to the evaluation. If possible, the same arm and equipment should be used for each evaluation. While in residence, blood pressure and pulse will be evaluated in the morning (prior to dosing on Days 1 and 3).
f Height/weight will be evaluated and BMI calculated at the screening visit. Only weight will be evaluated upon follow-up.
g A 12-lead ECG will be performed after the volunteer has rested in the supine position for 10 minutes prior to the evaluation.
h The volunteer will fast for at least 4 hours prior to clinical laboratory evaluations.
i Creatinine clearance will be estimated using the Cockcroft-Gault formula at screening and discharge.
j A serum pregnancy test at screening and a urine pregnancy test on Day -1 will be performed for all women of childbearing potential. If positive, the volunteer is excluded from participation in the study.
k Performed as appropriate to confirm postmenopausal status.
l Volunteers will be randomized in the morning of Day 1 just prior to IP administration.
m Crossover periods: Volunteers will receive a single, 60-minute infusion in each crossover period.
n Pharmacokinetic blood samples will be collected contralaterally from the dosing arm and appropriately processed at the following time points relative to the start of the infusion, unless otherwise indicated: predose (-60 to 0 minutes prior to the start of the iv infusion), 20 minutes, 40 minutes, end of infusion (within 2 minutes before the end of the infusion), 65 minutes, 75 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 18 hours and 24 hours postdose.
o SAEs will be collected from the time when informed consent is signed until the follow-up visit. Non-serious AEs will be collected from Day -1 of Period 1 until the follow-up visit.

3.2 Rationale for study design, doses and control groups

Ceftaroline fosamil 600 mg has been approved in the US and has been submitted to the European Medicines Agency for approval. To support 600 mg to be administered in a volume less than the standard 250 mL, Part A of this study is being carried out to look at local tolerability when diluted in lower volumes.

Part B of the study will be conducted to characterize the single-dose PK of ceftaroline, its prodrug (ceftaroline fosamil), and metabolite (ceftaroline M-1) at the same infusion regimens/volumes as the active treatments in Part A (600 mg ceftaroline diluted in volumes of either 50 mL and 250 mL, or 100 mL and 250 mL, as described in Section 5.8).

This study will be conducted in healthy adult volunteers to avoid interference from disease process or other drugs. The selection criteria are defined such that volunteers selected for participation in the study are known to be free from other clinically significant illness and have adequate veins on the back of both hands and both forearms to accommodate the simultaneous bilateral infusions for Part A.

This study will be conducted in 2 parts, customized to the respective primary objectives. The crossover design for both study parts allows each volunteer to be his/her own reference, as well as accounting for period effects, if they exist. The duration of the infusion administration period is to follow established practice guidelines which recommend that peripheral IV sites should be changed every 72 hours. A minimum one day washout (used in Part B) is sufficient considering ceftaroline t½ of approximately 2 to 3 hours. The washout period in Part A has been designed as a minimum of 4.5 days (approximately 108 hours) between treatments to allow any ISRs experienced by a subject in Period 1 to resolve prior to treatment in Period 2.

As the assessments for the primary PK objective are not subjectively biased, an open-label design for Part B is appropriate. In addition, an open-label design has the advantages of minimizing discomfort to the volunteers and reducing the number of PK samples associated with bilateral administrations of the active and placebo treatments required to maintain the blind of the different volumes being infused. The randomization will also be stratified by arm to avoid confounding arm with period effects and to reduce the potential for carryover effects due to ISRs or PK sampling.

To date, infusion volumes ranging from 175 mL to 270 mL have been used in the Phase I, II and III trials. All Phase III studies for both the cSSTI and CAP programs have only used a standard dose of 600 mg for subjects with normal or mild renal impairment and a dose of 400 mg for those with moderate renal impairment at concentrations ranging from of 1.5 to 2.7 mg/mL for the intravenous (iv) infusion solutions. However since doses used in the Phase 1 studies have varied more, the iv infusion concentrations administered have ranged from 0.3 to 8 mg/mL. The concentrations to be used in the current study are 2.4 mg/mL (250 mL volume), 12 mg/mL (50 mL volume), and if required, 6 mg/mL (100 mL volume).

Three studies in the rabbit to assess local tolerance were dosed using a concentrations of 4.2 mg/mL administered in the ear vein or 150 and 200 mg/mL administered intramuscularly.

In the 4-week monkey study (TAK599-00037) and 13-week rat and monkey studies (P0903-T-010 and P0903-T-011, respectively) the severity and incidence of microscopic findings at the infusion sites was similar across all groups, including controls, both at the end of the main test phase and at the end of the recovery phase. The high-dose groups were administered ceftaroline fosamil intravenously in concentrations of ceftaroline fosamil exceeding 12 mg/mL. Importantly, monkeys in the 4-week study were administered ceftaroline fosamil as 1-hour infusion into the saphenous or cephalic vein with no suggestion of major irritation issues in concentrations up to 80 mg/mL. In these studies, there was no evidence of haemolysis from haematology raw data.

The age range of the subjects is broad so that the study population will be reflective of the target therapeutic population.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the volunteer screening log, of volunteers who entered prestudy screening.

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

4.1 Inclusion criteria

For inclusion in the study volunteers should fulfill the following criteria:

Provision of informed consent prior to any study-specific procedures

1. Healthy male and/or female volunteers between the ages of 18 to 75 years, inclusive, with veins on the back of both hands and both forearms suitable for cannulation or repeated venipuncture. For Part A, volunteers must be willing to have both arms used during the study with catheters inserted for up to a maximum of 72 hours (6 infusions).

2. 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

3. Male volunteers must be willing to use barrier contraception ie, condoms, from the first day of dosing until 3 months after the last dose of IP.

4. Have a body mass index (BMI) between 18 and 30 kg/m2, inclusive, and weigh at least 50 kg

5. As judged by the Investigator, able to understand and be willing to communicate with the Investigator and comply with all the study requirements

4.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study (applies to AstraZeneca, Cerexa, Forest employees, their close relatives, and/or staff at the study site)

2. Previous randomization to treatment sequence in the present study

3. Use of any other investigational compound or participation in another clinical trial, within 3 months prior to first administration of IP in this study. The period of exclusion begins at the time of the last visit of the prior study. Volunteers consented and screened but not dosed in this study or previous Phase I studies are not excluded.

4. History of any clinically significant disease or disorder, eg, cardiac, neurological, hematological, psychiatric, gastrointestinal, hepatic, renal disease, or other condition which, in the opinion of the Investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study

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

6. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IP

7. Any clinically significant abnormalities in the physical examination, laboratory values, or 12-lead ECG, as judged by the Investigator

8. Abnormal vital signs, after 10 minutes supine rest, defined as any of the following:

- Systolic blood pressure >140 mm Hg
- Diastolic blood pressure >90 mm Hg

9. Any positive serology result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV), or human immunodeficiency virus (HIV)

10. Known or suspected history of drug abuse, as judged by the Investigator

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

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

13. Positive screen for drugs of abuse, or smokerlyzer test at screening or positive screen for drugs of abuse, alcohol breath test or smokerlyzer test on admission to the unit prior to the first administration of IP

14. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of any hypersensitivity or allergic reaction to any β-lactam antimicrobials or drugs with a similar chemical structure or class as ceftaroline

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

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

17. For Part B, plasma donation, or any blood donation, blood product donation, or blood loss greater than 500 mL during the 3 months prior to screening

18. Creatinine clearance of less than 80 mL/minute (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 in mg/dL

19. Judgement by the Investigator that the volunteer 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.

Procedures for withdrawal of incorrectly-enrolled volunteers are presented in 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 clinical laboratory evaluations

2. Eat and drink only the standardized meals and drinks provided (apart from water) during the residential periods in the unit

3. Abstain from consuming any of the following:

   - Alcohol from 72 hours before admission to the clinic, during each residential period, and for 72 hours before the study follow-up visit

   - Energy drinks containing taurine or glucuronolactone, eg, Red Bull from 72 hours before admission, during each residential period, and for 72 hours before the study follow-up visit

   - Caffeine- and xanthine-containing food and drink from 48 hours prior to infusion of the first dose and during each residential period, apart from any provided as part of a standardized meal. Excessive intake of caffeine should be avoided during the washout period (Part A) and between discharge from the unit and the study follow-up visit.

   - Poppy seeds found in specialty breads from time of consent until after the final medical examination at the study follow-up visit

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

5. Abstain from taking any medication, prescribed or over-the-counter products (other than paracetamol/acetaminophen or hormone replacement therapy), from 2 weeks prior to the first administration of IP until after the final medical examination at study 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.

6. Volunteers should refrain from strenuous physical activity, which is not within the volunteers' normal daily routine, from 7 days prior to first admission to the unit until after the final medical examination at the study follow-up visit

7. Volunteers participating in Part B of the study should abstain from blood or plasma donation from 3 months before screening until 3 months after screening

8. Male volunteers should use a condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm or fathering a child from the date of dosing until 3 months after dosing with the IP; 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. 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.

9. Remain in the unit during each residential period until all study assessments and procedures have been completed including completion of the 72-hour infusions (sixth final infusion set in Period 2) for Part A and collection of the 24-hour PK sample for Part B

5.2 Subject enrollment and randomization

The Investigator will:

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

2. Assign potential volunteer a unique enrollment number, beginning with 'E0001001'

3. Determine volunteer eligibility. See Sections 4.1 and 4.2.

4. Assign eligible volunteers a unique subject number, beginning with '1001'

If a volunteer withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

Procedures for randomization

Randomization schemes will be produced for each study part separately by using the global randomization system. Randomization will be performed on Day 1 just before administration of the IP. Randomization codes will be assigned strictly sequentially as volunteers become eligible for randomization.

For Part A, volunteers will be randomly assigned in a 1:1 fashion to 1 of 2 treatment sequences (to Sequence 1 or 2 or, in the event the 50-mL infusion volume is deemed poorly tolerated, to Sequence 3 or 4) of infusion volumes of ceftaroline fosamil 600 mg and placebo,

as outlined in Table 4 (see Section 3.1.1). These sequences avoid administering active treatment in the same arm for both treatment periods and administering the same volume to both arms within the same treatment period.

Table 4 Treatment arm randomization scheme

Sequence	Crossover period	Left arm	Right arm
Sequence 1	1	50 mL active (Treatment A)	250 mL placebo (Treatment D)
	2	50 mL placebo (Treatment B)	250 mL active (Treatment C)
Sequence 2	1	250 mL active (Treatment C)	50 mL placebo (Treatment B)
	2	250 mL placebo (Treatment D)	50 mL active (Treatment A)
Sequence 3	1	100 mL active (Treatment E)	250 mL placebo (Treatment D)
	2	100 mL placebo (Treatment F)	250 mL active (Treatment C)
Sequence 4	1	250 mL active (Treatment C)	100 mL placebo (Treatment F)
	2	250 mL placebo (Treatment D)	100 mL active (Treatment E)

Sequence 3 and Sequence 4 are conditional, as described in Section 3.1.1.

For Part B volunteers will be randomly assigned in a 1:1 fashion to either treatment sequence CA or AC. If Treatment A is shown to be poorly tolerated in Part A of the study, Treatment E will replace Treatment A in Part B, and the volunteers will be randomized 1:1 to treatment sequence CE or EC. The arm infused will switch from the first period to the second and thus the randomization will be stratified by the ordering of infusion (RL and LR), to balance any potential arm effects, and to avoid confounding arm with period effects.

5.3 Procedures for handling subjects incorrectly randomized

Volunteers who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

Where a subject, who does not meet the selection criteria, is randomised in error and this is identified before dosing, the subject should be withdrawn from the study. A discussion should occur between the CPA Physician and the Investigator regarding whether a replacement may be considered. The CPA Physician is to ensure all such decisions are appropriately documented.

Where subjects are enrolled but subsequently fail to meet the study criteria post initiation, a discussion should occur between the CPA Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

If a subject is withdrawn from study drug they should be advised to continue assessments for safety monitoring.

The CPA Physician is to ensure all such decisions are appropriately documented.
In situations where an agreement cannot be reached, the volunteer should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Part A of this study is double-blind with regard to treatment (ceftaroline or placebo). The following personnel will have access to the randomization list:

- The AstraZeneca personnel carrying out the labeling and packaging of IP
- The pharmacy personnel preparing and labelling IP at the site

The randomization 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.

Part B is open-label; therefore, no blinding procedures are needed.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized volunteer, will be available to the Investigator or pharmacist at the study center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the volunteer requires knowledge of the treatment randomization. The Investigator documents and reports the action to the Sponsors, without revealing the treatment given to the volunteer to the Sponsors' staff. Following completion of Part A, an unblinded review of the ISR incidence will be performed, as described in Section 5.8.

The Sponsors retain the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data (other than as described in Section 5.8) until all decisions on the evaluability of the data from each individual volunteer have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Ceftaroline fosamil	600 mg of ceftaroline fosamil a pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20 mL vial	

The formulation number and batch numbers will be recorded in the Study Master File and identified in the CSR.

Ceftaroline fosamil for infusion is supplied as 600 mg of ceftaroline fosamil (the prodrug of ceftaroline), a sterile pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20-mLvial. An excipient, L-arginine (approximately 660 mg L-arginine/g of prodrug) is added as an alkalizing agent to maintain the pH of the constituted solution to pH 4.8 to 6.2. The investigational site will be responsible for diluting the concentrate to obtain the desired infusion volume.

Placebo for Part A will consist of 0.9% sodium chloride infusion fluid of various infusion volumes (ie, 50, 100, or 250 mL) as appropriate.

The constitution time should be no more than 120 seconds. After constitution of ceftaroline fosamil vials, infusion solution preparation must be completed within 30 minutes. 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.

Reconstituted solutions and subsequent infusions should be prepared using standard aseptic techniques.

Those individuals involved in the drug-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.

Product preparation requirements

The following will be used to administer study drug:

Ceftaroline:

- Ceftaroline fosamil powder 600 mg containing L-arginine alkalizing agent

- Sterile water for infusion, USP
- 0.9% sodium chloride infusion fluid (50, 100, or 250 mL infusion bags, as appropriate)
- Standard catheters approved for use in both the US and EU

Placebo for Part A will consist of 0.9% sodium chloride infusion fluid (50, 100, or 250 mL infusion bags).

See Table 5 for the constitution of the ceftaroline fosamil and volume to be inserted into infusion bag. The extractable volume of the reconstituted vial should then be transferred to the 0.9% sodium chloride infusion bag to achieve the final bag volume.

Table 5 Concentration and extractable volumes of reconstituted active drug

Active drug	Volume of water required for reconstitution of vial	Extractable volume of reconstituted vial	Solution concentration
Ceftaroline fosamil 600 mg	20.0 mL	20.7 mL	29 mg/mL

Further instructions regarding dose preparation, blinding, and administration will be documented in separate pharmacy handling instructions.

5.5.2 Doses and treatment regimens

During Part A, each volunteer will receive simultaneous bilateral iv infusions of IP (ceftaroline fosamil 600 mg in 1 arm and placebo in the other arm) over 60 minutes every 12 hours for a maximum of 72 hours (6 infusions). Volunteers will then enter a minimum 4.5-day (approximately 108 hours) washout period before crossing over and receiving simultaneous bilateral iv infusions of IP (ceftaroline fosamil 600 mg in the contralateral arm from Period 1 and placebo in the other arm), in veins different than those used previously, over 60 minutes every 12 hours for a maximum of 72 hours (6 infusions). Should the volunteer experience an ISR of 2 or greater as measured by the Visual Infusion Phlebitis (VIP) scale (see Appendix D), the infusion must be stopped on that arm (ie, the cannula will not be resited for that treatment period) and the ISR will be recorded as an AE. The infusion on the other arm will continue, as appropriate. See Section 5.8 for study stopping criteria and Section 3.1.1 for a description of treatments and treatment sequences.

In Part B, each volunteer will receive a single dose of 600 mg ceftaroline fosamil infused over 60 minutes in each crossover period (Days 1 and 3). See Section 3.1.2 for a description of treatments.

Catheters should be standardized and approved for use in both the US and EU. For each crossover portion, catheters should be inserted into the same ‘anatomical site’, preferably hand and forearm, with care taken to minimize cannula placement in the wrist or antecubital fossa.

Cannula insertion must be performed by a qualified health care professional. Aseptic technique must be used and standard precautions observed prior to and during vascular access placement. This includes the appropriate use of hand hygiene, glove selection, glove use, and decontamination of the peripheral catheter site with individually packaged alcohol wipes. Please note, only alcohol wipes are to be used to clean the site of catheter placement. Peripheral vascular access catheter placement will be documented for each volunteer in a separate source document. Information recorded will include batch number, gauge and length, number of attempts, anatomical location, and volunteer's response to placement. Care of the catheter site and restrictions are specified in advance. The mechanics of line clearance post infusion should be carefully considered.

For dosing in both study parts and for all infusions, the date and time of the infusion start and stop as well as the start and stop of any infusion interruption and restart of the infusion, and the actual volume and amount of ceftaroline fosamil infused will be recorded. In addition, the arm (left or right) in which the infusion is administered will be documented.

5.5.3 Additional study drug (not applicable)

5.5.4 Labelling

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

5.5.5 Storage

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

Vials of ceftaroline fosamil for injection dry mixture should be stored at 2° to 8°C until ready for use. Vials should be used before the labeled expiry date.

5.6 Concomitant and poststudy treatment(s)

Apart from paracetamol/acetaminophen and hormone replacement therapy, no concomitant medication or therapy will be allowed. The volunteers 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 volunteer's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the case report form (CRF). When any medication is required, it should be prescribed by the Investigator who should inform the CPA Physician. Following consultation with the CPA Physician, the Investigator should determine whether or not the volunteer should continue in the study.

5.7 Treatment compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the CRF.

Treatment compliance will be assured by supervised administration of the IP by the Investigator or delegate. The dose, dates, and times of administration of the IP will be recorded and will be checked by the monitor at monitoring visits.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The study centre personnel will account for all investigational products received at the study center, unused investigational product and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.8 Discontinuation of investigational product and withdrawal from study

Volunteers may be discontinued from IP in the following situations:

- Volunteer decision. The volunteer is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event
- Severe noncompliance to this CSP as judged by the Investigator and/or AstraZeneca
- Randomization in error (see Section 5.3)
- Catheter becomes dislodged or is removed from either arm prior to scheduled time point

Dosing for any individual volunteer will be stopped if the volunteer experiences a possibly drug-related SAE or a possibly drug-related significant nonserious AE, which in the opinion of the Investigator or Sponsor, warrants discontinuation from the study for that volunteer's well being.

Volunteers who have a VIP score of 2 or more will not have any further infusions in the affected arm for that treatment period. For Part A, if the infusion site in the contralateral arm is healthy, the infusions may continue in that arm.

Stopping criteria for Part A

Dosing will stop with an infusion volume (50, 100 or 250 mL) if any of the following scenarios occur with a reasonable possibility of a causal relationship with the investigational product:

- Two or more subjects report a serious adverse event (SAE) or have a VIP score of 5
- Four or more subjects have a VIP score of 4

During Part A of the study data will be reviewed by the Investigator on an ongoing basis. If 15 or more subjects develop ISRs, but the stopping criteria listed above have not been met, the Investigator may request an independent unblinded review of the available safety and tolerability data. If once unblinded the incidence of ISRs on any active volume is >40% of the total anticipated recruitment for Part A, an ad hoc data review meeting will be arranged between the Investigator, Sponsor, and other team members, as applicable, to determine study termination. Otherwise, dosing will be continued as planned in the remaining 50 mL subjects.

At completion of Treatment A (50 mL infusion volume), an unblinded review of the ISR incidence will be performed by a person who is not involved with the conduct of the study. If the cumulative ISR incidence is ≤40% in both active treatments for the 50-mL and 250-mL infusion volume (Treatments A and C) as determined by the unblinded reviewer, the Investigator and Sponsor will be notified, and the study will proceed to Part B. However, if the cumulative ISR is >40% for the 50-mL active treatment (Treatment A) but is ≤40% for the 250-mL active treatment (Treatment C), after review in the context of the corresponding placebo findings and following discussion with the Sponsor, Part A may be repeated with the 100-mL and 250-mL while Part B will be pending until after data review of the last cohort in Part A . In the instance of being repeated with 100 mL, the data review and study termination procedures in Part A will then be applied to the 100-mL treatment. At the completion of the last cohort for the 100-mL and 250-mL evaluation in Part A, if the cumulative ISR is ≤40% in both active treatments for the 100-mL and 250-mL infusion volume (Treatments E and C) as determined by the un-blinded reviewer, the Investigator and Sponsor will be notified, and the study will proceed to Part B which will include Treatment E and Treatment C.

Procedures for discontinuation of a subject from investigational product

Volunteers are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such volunteers will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up. See Sections 6.3.4 and 6.3.5.

Additional volunteers may be enrolled at the discretion of the Sponsor if the number of evaluable volunteers is not sufficient for either study part.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below and the timing of these assessments are detailed in Table 2 and Table 3 for Parts A and B, respectively.

It is important that PK sampling during Part B occurs as close as possible to the 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. 12-lead ECG
2. Blood pressure and pulse rate
3. PK blood sample (Part B only)
4. Other safety and laboratory assessments
5. Volunteers will fast for at least 4 hours prior to the clinical laboratory evaluations.

6.1 Recording of data

The Phase I electronic data capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the CRFs as specified in this CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study center.

6.2 Data collection and enrollment

6.2.1 Screening procedures

For both study parts, each volunteer will undergo screening during the 28 days prior to admission to the study center to confirm eligibility. This will consist of:

- Obtaining written informed consent before starting any study-specific procedures
- Recording of demographic data (date of birth, sex, and race)
- A standard medical, medication, and surgical history as well as smoking history with review of the inclusion and exclusion criteria with the volunteer
- A complete physical examination (see Section 6.3.7)
- Height (in cm), weight (in kg), and calculation of BMI
- Vital signs (resting supine blood pressure and pulse rate)
- Recording a resting 12-lead paper ECG

- Following a minimum 4-hour fast, blood samples will be collected for routine clinical chemistry (including serum pregnancy tests for female subjects and FSH for females only to confirm postmenopausal status), hematology, and screening for HBsAg, HCV, and HIV
- A urine sample for routine urinalysis (including microscopic examination), drugs of abuse screen
- Alcohol breath test and smokerlyzer test
- Creatinine clearance estimation
- Concomitant medication use
- Recording of SAEs

After admission and before randomization the Investigator should reassess each volunteer to reconfirm eligibility.

6.2.2 Follow-up procedures

A poststudy medical examination will be performed 5 to 10 days after discharge from the study center (Day 4 of Period 2 for Part A, or Day 4 of Part B). These assessments will include supine blood pressure and pulse; weight; clinical chemistry, hematology, and urinalysis; and recording of concomitant medications and AEs. The volunteers will be fasted for 4 hours prior to follow-up procedures.

6.3 Safety

The Investigator is responsible for ensuring that all staff involved in the study are 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 D. These assessments will occur as specified in Section 3.1.1. 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 D.

For those volunteers who experience an ISR, their washout period may be extended to allow recovery of the infusion site.

6.3.2 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a preexisting 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 and ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.3.3 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the volunteer 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 definition of other significant AE (OAE) see Section 11.1.2.

6.3.4 Recording of adverse events

Time period for collection of adverse events

SAEs will be collected from the time when informed consent is signed until the follow-up visit. Non-serious AEs will be collected from the first admission to the clinical unit until the follow-up visit.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the volunteer'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 volunteer 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:

- Adverse event diagnosis/description
- Date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Adverse event caused volunteer'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:

Mild (awareness of sign or symptom, but easily tolerated)

Moderate (discomfort sufficient to cause interference with normal activities)

Severe (incapacitating, with inability to perform normal activities)

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 IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

Adverse events based on signs and symptoms

All AEs spontaneously reported by the volunteer or reported in response to an open question from the study personnel eg '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 summarized in the 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 fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically-relevant deteriorations in nonmandated 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.

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 Investigators or other site personnel inform appropriate AstraZeneca representatives within 1 day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

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

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

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

6.3.6 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the study plan (see Table 2 and Table 3). The date and time of collection of all laboratory tests will be recorded in the appropriate CRF. Volunteers will fast for 4 hours prior to the clinical laboratory evaluations. Laboratory variables to be measured are shown in Table 6.

Table 6 Safety laboratory variables

Haematology	Clinical chemistry	Urinalysis
Blood (B)-hemoglobin	Serum (S)-albumin	Urine (U)-glucose
B-platelet count	S-alanine aminotransferase	U-hemoglobin
B-absolute leukocyte differential count[a]	S-aspartate aminotransferase	U-protein
B-leukocyte count	S-alkaline phosphatase	Microscopic examination[b]
B-reticulocytes	S-bilirubin, total	
B-erythrocytes	S-calcium, total	
B-hematocrit	S-creatinine	
B-erythrocyte mean cellular volume	S-glucose	
	S-potassium	
	S-sodium	
	S-total protein	

[a] The leukocyte differential count will include: neutrophils, eosinophils, basophils, lymphocytes, and monocytes.
[b] All urine samples will be evaluated microscopically.

Creatinine clearance will be estimated using the Cockcroft-Gault formula (see Section 4.2) at screening and at clinic discharge on Day 4 of Period 2 for Part A and Day 4 for Part B.

Additionally, at screening all volunteers will be tested for HIV, HBsAg, and antibodies to HCV. If indicated for females, FSH will be measured to determine their menopausal status at screening. Urine will be tested for drugs of abuse at screening and admission to the study

center on Day -1 including amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, phencyclidine, tetrahydrocannabinoid, benzodiazepines, and opiates. For female volunteers a serum pregnancy test will be performed at screening and a urine test on each admission to the study center (Day -1).

Alcohol breath test and smokerlyzer test will be conducted at screening and admission Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Volunteers in whom suspected values of clinical significance are confirmed will either not be included in the study or, if already randomized, will be followed until normalization or for as long as the Investigator considers necessary. Additional laboratory assessments may be performed for safety reasons if judged appropriate by the Investigator.

The safety laboratory samples will be analyzed using routine methods at the local safety laboratory of the study center.

For AEs based on laboratory tests, see Section 6.3.4. For blood volumes, see Section 7.1.

6.3.7 Physical examination

A complete physical examination will be performed at screening, Day -1, and at each clinic discharge and includes an assessment of the following: general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, respiratory, and neurological systems. During the washout period of Part B, prior to dosing, a brief physical examination is required.

Height will be measured in centimeters and weight in kilograms. Measurements should be taken without shoes and, if possible, the same scale used for all measurements. Body mass index will be calculated from the height and weight at screening.

For AEs based on examinations and tests, see Section 6.3.4.

6.3.8 ECG

A 12-lead resting paper ECG will be recorded on the days indicated in the study plan (Table 2 and Table 3). Volunteers must rest in a supine position for 10 minutes before each assessment. Overall evaluation (normal/abnormal) will be recorded in the CRF. If the ECG is abnormal, the abnormality and its clinical significance will be specified in the CRF.

The print-out of the ECG is to be signed, dated, and filed in the Investigator's Study File along with a signed and dated copy (if the print-outs are not on archive-quality paper).

For AEs based on examinations and tests, see Section 6.3.4.

6.3.9 Vital signs

Supine blood pressure and pulse will be measured using noninvasive equipment after the volunteer has rested at least 10 minutes in a supine position. If possible, the same arm and equipment should be used for each evaluation. While in residence, blood pressure and pulse

will be evaluated in the morning. For timing of assessments refer to Table 2 and Table 3 for Parts A and B, respectively.

For AEs based on examinations and tests, see Section 6.3.4.

6.4 Pharmacokinetics

6.4.1 Collection of samples

Pharmacokinetic data will be collected in only Part B of this study.

At each time point presented in Table 3, 1 venous blood sample (approximately 4 mL per sample) will be collected contralaterally from the dosing arm for the determination of ceftaroline fosamil (the prodrug of ceftaroline), ceftaroline, and ceftaroline M-1 (the metabolite of ceftaroline) concentrations in plasma.

The sampling date and time will be recorded for all samples. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

For blood sample volumes to be collected, 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 will be analyzed by a designated laboratory 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 the time of receipt by the bioanalytical laboratory will be analyzed.

6.5 Pharmacodynamics (Not applicable)

6.6 Pharmacogenetics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each volunteer in this study is presented in Table 7.

Table 7 Volume of blood to be drawn from each subject

			Part A		Part B	
Assessment		**Sample volume (mL)[a]**	**No. of samples**	**Total volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	2.5	6	15	4	10
	Hematology	2	6	12	4	8
	Serology, serum pregnancy test and FSH	2.5	1	2.5	1	2.5
Pharmacokinetic	ceftaroline fosamil, ceftaroline, and ceftaroline M-1	4	0	0	30	120
Total				29.5		140.5

a If a cannula is used, an additional 1 mL of blood will be collected to flush the cannula.
b Pregnancy test and FSH in female subjects only; FSH will be assessed if indicated to determine volunteer's menopausal status

The number of samples collected, as well as the volume required for each analysis, may be changed during the study as new data on ceftaroline fosamil become available. However, the maximum volume to be drawn from each volunteer will not exceed 450 mL, ie, approximately the same volume as would be drawn during a regular blood donation.

7.2 Handling, storage, and destruction of biological samples

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

7.2.1 Safety samples

Safety samples will be used up, or disposed of after analysis.

7.2.2 Pharmacokinetic and/or pharmacodynamic samples

Samples will be used up, or disposed of after the CSR has been finalized, unless retained for future analyses.

Additonal analyses may 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 reproductibility of the method and will be reported in a separate table in the bioanalytical study contribution 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 of this CSP 'International Airline Transportation Association (IATA) 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not to be shipped and no further samples will be taken from the volunteer 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 lifecycle.

The Investigator keeps full traceability of collected biological samples from the volunteers while in storage at the center 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, disposed of, or until further shipment, and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca bio bank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

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

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site

- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

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

The Ethics Committee 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 volunteers. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any volunteer into the study.

The Ethics Committee should approve all advertising used to recruit volunteers for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the CSP should be reapproved by the Ethics Committee annually.

Before enrollment of any volunteer 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 the Regulatory Authority, Ethics Committee, and Principal Investigator with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

8.4 Informed consent

The Investigator will:

- Ensure that each volunteer is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure that each volunteer is notified that they are free to withdraw from the study at any time
- Ensure that each volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each volunteer 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 volunteer
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

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, 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 Ethics Committee 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 protocol to the Investigator. For distribution to the Ethics Committee see Section 8.3.

If a protocol amendment requires a change to the Informed Consent Form, AstraZeneca and the Ethics Committee 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 Ethics Committee.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, 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, analyzed, and accurately reported according to the CSP, ICH/GCP guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT

9.1 Prestudy activities

Before the first volunteer is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate volunteers for the study
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and the responsibilities of AstraZeneca or their representatives.

9.2 Training of study site personnel

Before the first volunteer is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures.

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 site, including visits to:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team 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 study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the volunteer's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating volunteers. This will require direct access to all original records for each volunteer (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the volunteer's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the volunteer

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center need information and advice about the study conduct.

9.3.1 Source data

The location of data identified as source will be provided in a source data identification document provided by .

9.4 Study agreements

The Investigator should comply with all the terms, conditions, and obligations of the CSA or equivalent for this study. In the event of any inconsistency between this CSP and the CSA, the CSP shall prevail with respect to the conduct of the study and the treatment of volunteers and in all other respects, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Investigator should be in place before any study-related procedures can take place or volunteers are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last volunteer undergoing the study'.

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

The data in this study will be collected using paper CRFs.

When the completed paper CRF 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

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

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

When all data have been coded, validated and signed the database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca as described in the Laboratory Manual.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Calculation of change from baseline

Change-from-baseline values will be calculated for the variables listed below, as the posttreatment value minus the value at baseline. The baseline values for both Part A and Part B will be as follows:

- Clinical laboratory tests: Day -1

- Vital signs (supine): Day 1 predose

If a volunteer is missing the baseline collection, the previous nonmissing evaluation will become the baseline value. If no baseline or previous-to-baseline value exist, then the baseline value will be treated as missing and no changes from baseline will be calculated.

11.1.2 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 or AEs leading to discontinuation of IP and withdrawal from the study. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs, and other safety assessments will be performed for identification of OAEs.

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

11.2 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic analysis of the plasma 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 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 units of hour for PK protocol time points that are in units of minute (including 20-, 40-, 60-, 65-, 75-, and 90-minute plasma PK samples). These derived nominal time points will be rounded to 2 decimal places.

Pharmacokinetic parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 5.2, or higher, (Pharsight Corp., Mountain View, California, US) or SAS® Version 9.2, or higher (SAS Institute Inc., Cary, North Carolina, US). All PK computations will be performed using WinNonlin® Professional Version 5.2, or higher; or SAS® Version 9.2, or higher. Graphics may be prepared with SAS® Version 9.2, or higher; or SigmaPlot® 9.0, or higher (Systat Software Inc., San Jose, California, US).

Where estimable, the following single-dose PK parameters will be calculated for ceftaroline fosamil, ceftaroline, and ceftaroline M-1 from plasma concentrations collected following dosing in each period (Days 1 and 3):

- Maximum plasma concentration (C_{max}, μg/mL), obtained directly from the observed concentration versus time data

- Time to maximum concentration (t_{max}, h), obtained directly from the observed concentration versus time data

- Area under the plasma concentration-time curve from zero to infinity (AUC, µg·h/mL), calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0-t)}+ C_{last}/\lambda_z$. If the extrapolated area (C_{last}/λ_z) is greater than 20% of AUC, then AUC and related parameters will be not reported.

- Area under the plasma concentration-time curve from zero to time of the last quantifiable concentrations ($AUC_{(0-t)}$, 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)

- Apparent terminal elimination rate constant (λ_z, 1/h)

- Half-life associated with the terminal slope ($t_{½\lambda z}$, h), determined as $\ln(2)/\lambda_z$

- Mean residence time (MRT, h)

- Total body clearance of drug from plasma (CL, L/h) (for ceftaroline fosamil and ceftaroline [apparent CL])

- Volume of distribution based on the terminal phase (V_z, L) (for ceftaroline fosamil and ceftaroline [apparent V_z])

- Volume of distribution at steady state (V_{ss}, L) calculated as the product of MRT and CL for nonsteady-state data (for ceftaroline fosamil and ceftaroline [apparent V_{ss}])

- C_{max} ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,Cmax}$) (adjusted for differences in molecular weights)

- AUC ratios of ceftaroline/ceftaroline fosamil and ceftaroline M-1/ceftaroline ($R_{M/D,AUC}$) (adjusted for differences in molecular weights)

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.

Individual ratios of Treatment A/Treatment C (or Treatment E/Treatment C, if applicable) will also be calculated for ceftaroline AUC, $AUC_{(0-t)}$, $AUC_{(0-12)}$, and C_{max}.

The following PK parameters will be calculated for diagnostic purposes and will be listed, but not summarized:

- The time interval (λ_z upper and lower) of the log-linear regression to determine $t_{½\lambda z}$

- Number of data points (λ_z, N) included in the log-linear regression analysis
- Goodness-of-fit statistic for calculation of λ_z (Rsq)
- The percent of AUC which is extrapolated to infinity (AUC_{ex}, %)

A minimum of 3 data points and an Rsq value of >0.8 will be used as the criteria for reliable estimation of λ_z.

Due to collection of a blood sample at the end of the infusion, no additional calculation of a concentration at the end of infusion will be performed. The decision to impute a missing end-of-infusion value, or if there is a large time deviation associated with the end-of-infusion sample, will be made on a case-by-case basis per Standard Operating Procedures and Work Instructions. The approach applied in the analyses will be documented in the CSR.

11.3 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 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, volunteers who receive treatment other than the one designated in the randomization schedule will be analyzed by actual treatment and not by randomized treatment.

12.1.2 Analysis of safety population

All volunteers who receive at least 1 dose of randomized IP, ceftaroline fosamil or placebo, and for whom any postdose data are available, will be included in the safety population.

12.1.3 Pharmacokinetics analysis set

The PK analysis set will include all volunteers who receive at least 1 dose of ceftaroline fosamil and have at least 1 measured concentration of any of the 3 analytes in plasma 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 or violations thought to significantly affect the PK of the IP) from all volunteers who received IP.

12.2 Methods of statistical analyses

12.2.1 General principles

Given the exploratory nature, no formal statistical hypothesis testing will be performed in this study. Standard Operating Procedures and Work Instructions will be used as the default methodology if not otherwise specified.

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

Results from both Part A and Part B will included in the clinical study report.

12.2.2 Subject characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum). Categorical variables will be summarized in frequency tables (frequency and proportion). Tabular summaries will be presented for all Part A and Part B volunteers overall.

12.2.3 Safety and tolerability

Continuous variables (clinical chemistry, hematology, and vital signs) will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) by scheduled time point. Categorical variables (AEs and urinalysis) will be summarized in frequency tables (frequency and proportion).

For Part A, systemic AEs will be summarized by the active treatment received in the respective treatment period (ie, ceftaroline fosamil 600 mg in either 50 or 250 mL infusion volumes). Clinical laboratory and vital sign parameters will be summarized by scheduled assessment (Day -1 to follow-up) for all Part A volunteers overall.

For Part B, AEs will be presented by treatment (ie, ceftaroline fosamil 600 mg in 50, 100, or 250 mL infusion volumes, as applicable). Clinical laboratory and vital sign parameters will be summarized by scheduled assessment (Day -1 to follow-up) for all Part B volunteers overall.

SAEs will be collected from the time when informed consent is signed until the follow-up visit. Non-serious AEs will be collected from Day -1 (first admission period) until the follow-up visit. Adverse events that occur before the first dose of IP will be listed and flagged, but will not be included in the tabular summaries of AEs.

Adverse events will be presented by preferred term and system organ class according to MedDRA classification. Listings of SAEs and AEs that led to withdrawal will be presented and the number of volunteers who had any AEs, SAEs, AEs that led to withdrawal, AEs

judged as causally related to IP by the Investigator, and AEs with severe intensity will be summarized.

Electrocardiogram and physical examination findings will be listed only.

12.2.4 Pharmacokinetics

Individual blood sample collection times, derived sampling time deviations, and concentration-time data will be listed. Pharmacokinetic data will be presented by analyte and treatment (Treatment A or E and Treatment C), as appropriate. Rounding conventions will follow Standard Operating Procedures and Work Instructions.

Plasma concentrations of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 will be reported to the same precision as the source data. Plasma concentrations will be summarized by nominal time point using descriptive statistics including the population size (N for sample size and n for available data), geometric mean, geometric coefficient of variation (CV%), arithmetic mean, SD, median, minimum, and maximum.

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 maximum value will be reported from the individual data, and the minimum and median will be set to BLQ.
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be reported for SD and CV% and BLQ will be reported for mean, geometric mean, minimum, median, and maximum.
- The number of BLQ values (n below LLOQ) will be reported for each time point.

Plasma PK parameters and ratios will be summarized by analyte and treatment as appropriate using descriptive statistics including: N, n, geometric mean, CV%, arithmetic mean, SD, median, minimum, and maximum.

Individual and summarized concentration-time profiles will be depicted on linear and semi-logarithmic scales by analyte and/or treatment. Plots of geometric mean and individual

values versus treatments will be presented for ceftaroline AUC, $AUC_{(0-t)}$, $AUC_{(0-12)}$, and C_{max}. Additional graphical presentations of data will be presented as deemed appropriate.

12.2.5 Pharmacodynamics (Not applicable)

12.2.6 Infusion Site Reactions (Part A Only)

The occurence of ISRs will be listed with VIP score by infusion volume/treatment combination across all assessments.

ISR incidence (number and percent of subjects) will be presented by infusion volume (50, 100, or 250 mL) and treatment (ceftaroline fosamil or placebo) combination. Incidence will also be cross-tabulated as occurrence (yes/no) across for active vs. placebo by infusion volume and treatment.

Placebo 50 mL will be presented separately to placebo 250 mL to allow the active incidence to be contrasted with its corresponding placebo.

12.3 Determination of sample size

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. A sample size of 24 volunteers is considered sufficient to assess if the low-volume infusion produces an increase in the incidence of ISRs (>40%). Therefore, approximately 32 volunteers will be recruited for Part A of this study to ensure the collection of complete data. This sample size is also sufficient to provide adequate safety data in healthy volunteers of the infusion volumes and placebo.

The PK profiles of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 following a single-dose iv administration of 600 mg ceftaroline fosamil (diluted in 250 mL) over 60 minutes have been characterized in previous studies. In Part B of the current study, although the infusion volumes will be different, this same dose and infusion duration will be administered across treatments and no major differences in exposures are expected. Data collected from approximately 8 volunteers is deemed adequate to characterize the PK of the 3 analytes in Treatment A (or Treatment E) and Treatment C.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.5.**

In the case of a medical emergency the Investigator may contact the CPA Physician. If the CPA Physician is not available, contact the CPA Program Director as detailed below.

Name	Role in the study	Address & telephone number

13.2 Overdose

No specific information is available on the treatment of overdosage with ceftaroline fosamil. 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.

13.3 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.

13.3.1 Maternal exposure

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

13.3.2 Paternal exposure

Pregnancy of a volunteer's partner is not considered to be an AE. However, any conception occurring from the date of dosing until 3 months after dosing should be reported to AstraZeneca and followed up for its outcome.

14. LIST OF REFERENCES (NOT APPLICABLE)

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.

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
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"

Appendix E

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