AstraZeneca

PROTOCOL SYNOPSIS

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

Study centre(s) and number of subjects planned

This will be a single centre study. Approximately 24 healthy Chinese volunteers, male and female, will be recruited in two groups to obtain at least 10 evaluable volunteers for each group. The groups will be recruited sequentially. An evaluable subject is defined as a volunteer completing all study procedures from the screening period to the final blood sampling time-point for plasma levels of ceftaroline on Day 10（Group I) or Day 9 (Group II).

Study period		Phase of development
Estimated date of first subject enrolled	Q4 2011	I
Estimated date of last subject completed	Q1 2012	I

Objectives

Primary Objective

- To characterize the pharmacokinetics of ceftaroline in healthy Chinese volunteers following single and multiple administration of 600 mg ceftaroline fosamil as 60-minute intravenous (IV) infusion every 12 hours(q12h) and as 120-minute intravenous infusion every 8 hours (q8h).

Secondary Objective

- To evaluate the safety and tolerability of ceftaroline in healthy Chinese volunteers following single and multiple administration of 600 mg ceftaroline fosamil as 60-minute IV infusion q12h and as 120-minute intravenous infusion q8h.

- To characterize the pharmacokinetics of ceftaroline fosamil and the ceftaroline metabolite (ceftaroline M-1) in healthy Chinese volunteers following administration of single and multiple 600 mg ceftaroline fosamil as 60-minute IV infusion q12h and as 120-minute intravenous infusion q8h.

Study design

This is a Phase I, open-label, single-centre Pharmacokinetic (PK) study, to characterize the safety and pharmacokinetics of ceftaroline following single and multiple dose administration of 600 mg Ceftaroline fosamil as 60-minute IV infusion q12h and as 120-minute intravenous infusion q8h in healthy male and female Chinese volunteers. The study will consist of a screening visit (Day -21 to Day -2) where subjects will undergo screening assessments preceding administration of the first dose of study drug on Day 1. Subjects will report to the Clinical Pharmacology Unit (CPU) the day before administration of the first dose of study drug (Day -1) and will remain confined there until completion of study procedures on Day 10 （Group I) or Day 9(Group II). In addition, subjects will return to the CPU for a follow up visit approximately 5-10 days after the discharge from the CPU. Each subject's participation, including the screening period, will take approximately 41 (Group I) or 40 (Group II) days.

This study will be conducted in two groups of healthy volunteers. The groups will be recruited sequentially.

Group I: 12 healthy volunteers will receive a single 600 mg ceftaroline fosamil as 60-minute IV infusion in the morning on Day 1 and 8. On Days 3 -7 the volunteers will receive 600 mg ceftaroline fosamil as 60-minute IV infusion q12h. On Day 2， the volunteers will not receive drug, but plasma and urine PK sample will be obtained.

Group II: 12 healthy volunteers will receive a single 600mg ceftaroline fosamil as 120-minute IV infusion in the morning on Day 1 and 8. On days 2 -7 the volunteers will receive 600mg ceftaroline fosamil as 120-minute IV infusion q8h.

Plasma and urine PK samples will be obtained at the times noted in Table 2.

Group I: Plasma and urine PK samples will be obtained following the first (Day 1) and last (Day 8) doses of study medication. In addition, at pre-dose of the first daily dose on Days 3-7, plasma PK samples will be obtained.

Group II: Plasma and urine PK samples will be obtained following the single dose on Day 1, and the last dose on Day 8 of study medication. In addition, at pre-dose of the first daily dose on Day 2 through Day7, plasma PK samples will be obtained.

Safety assessments including physical examinations, laboratory assessments, electrocardiograms (ECGs), and vital sign measurements will be performed according to the schedule (Table 1) for all healthy volunteers.

Principal investigator and AstraZeneca appropriate personnel will review the safety data after Group I last subject out, to determine if the next sequential cohort (Group II) may be enrolled as planned. The safety data (including all adverse events and laboratory data collected during the Group I drug administration phase) will be summarized and made available to the ethics committee for endorsement prior to the start of the enrolment of subjects in Group II.

Target subject population

Healthy male and female Chinese volunteers aged 18 to 45 inclusive.

Investigational product, dosage and mode of administration

Ceftaroline fosamil for injection is supplied as 600 mg of the prodrug of ceftaroline, a sterile, pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20 mL vial. An excipient, L-arginine (approximately 660 mg L-arginine/g of ceftaroline prodrug), is added as an alkalizing agent to control pH of the constituted solution to pH 4.8 to 6.2.

Each volunteer in Group I will receive a single 600 mg ceftaroline fosamil as 60-minute IV infusion in the morning on Days 1 and 8 , and will receive 600 mg ceftaroline fosamil as IV infusion over 60 minutes q12h on Days 3 -7.

Each volunteer in Group II will receive a single 600mg ceftaroline fosamil as 120-minute IV infusion in the morning on Day 1 and 8. On days 2 -7 the volunteers will receive 600mg ceftaroline fosamil as 120-minute IV infusion q8h.

Duration of treatment

Screening assessments for subject eligibility will occur within 21 days of administration of first dose of study drug.

Subjects will report to the study unit the day before the first dose of study drug is administered (Day –1). The subjects in both study groups will receive their first dose of ceftaroline fosamil in the morning on Day 1 and have the last plasma sample taken on Day 10 (Group I) or Day 9 (Group II). Subjects will remain confined in the study unit until procedures are completed on Day 10 (Group I) or Day 9 (Group II). In addition, subjects will return to the CPU for a follow up visit approximately 5-10 days after the discharge from the CPU. The duration of study participation will be approximately 41 (Group I) or 40 (Group II) days including the 21-day screening period.

Outcome variable(s):

Plasma PK Variable

- Single dose: AUC, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, C_{max}, T_{max}, CL, MRT, T? V_{ss} ,V_z and Kel
- Multiple dose: AUC, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$,$C_{ss,\,max}$, $C_{ss,\,min}$, $C_{ss,\,av}$, T_{max}, CL, MRT, T4, V_{ss}, Vz, $AR_{(Cmax)}$, $AR_{(AUC)}$, Kel, TCP and DF

Urine PK Variable

- A_e, f_e and CL_R

Safety Variable

- Adverse events, vital signs, ECG, laboratory values, physical exams

Statistical methods

Given the exploratory nature, no formal sample size calculation was made for this study and no formal hypothesis testing will be performed. A sample size of 10 evaluable healthy volunteers for each group is considered sufficient to characterize the PK characteristics and provide safety, and tolerability data in healthy volunteers.

To achieve the primary and secondary objectives in PK, the PK of ceftaroline, ceftaroline fosamil and ceftaroline M-1 will be evaluated by assessment of drug concentrations in plasma and urine. These drug concentrations will be listed and summarised for each dosing period using the geometric mean (Gmean), coefficient of variation (CV), arithmetic mean, standard deviation (SD), minimum, maximum, number of observations and number of observations $\geqslant$ LLOQ. The PK parameters except for Tmax will be summarised for each group using Gmean, CV, arithmetic mean, SD, minimum, maximum, number of observations. Tmax will be summarised for each group using median, minimum, maximum and number of observations.

To achieve the secondary objective in safety and tolerability, adverse events (AEs), vital signs, physical examinations, ECGs and clinical laboratory assessments at specific time points (Table 1) will be evaluated. All safety data will be summarized in a descriptive analysis. Baseline will be the last assessment before dose. All AEs will be summarised for each dose group by preferred term and system organ class of the current MedDRA dictionary for the dosing period. All serious AEs and discontinuations from investigational treatment will be summarised using the current MedDRA dictionary, as well as provided individual narratives and/or line listings.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse Event (see definition in Section 6.3.1)
A_e	Cumulative amount of unchanged drug excreted into the urine
ALT	Alanine aminotransferase
$AR_{(Cmax)}$	Accumulation ratio calculated from C_{max}
$AR_{(AUC)}$	Accumulation ratio calculated from AUC
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve from zero to infinity
$AUC_{(0-\tau)}$	Area under the plasma concentration-time curve from time zero to the end of dose interval for a repeated dose regimen
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time zero to time of last quatifiable plasma concentration
BMI	Body Mass Index
CABP	Community Acquired Bacterial Pneumonia
CL	Clearance
CL_{CR}	Creatinine Clearance
CL_R	Renal Clearance
C_{max}	Maximum (peak) plasma concentration
C_{min}	Minimum (minimum) plasma concentration
CRF	Case Report Form (Electronic/Paper)
CS	Clinically significant
CSA	Clinical Study Agreement
CSR	Clinical Study Report
cSSSI	Complicated Skin and Skin Structure Infection
CTCAE	Common Terminology Criteria For Adverse Event
CPU	Clinical Pharmacology Unit
$C_{ss, av}$	Average drug concentration in plasma during a dosing interval at steady state [amount/volume]
$C_{ss, max}$	Maximum (peak) steady state drug concentration in plasma during dosing interval [amount/volume]

Abbreviation or special term	Explanation
$C_{ss, min}$	Minimum (trough) steady state drug concentration in plasma during dosing interval [amount/volume]
CV	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse event
DF	Degree of fluctuation
DNA	Deoxyribonucleic Acid
DILI	Drug-induced liver injury
DMC	Data Management centre
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
f_e	Fraction of intravenously administered drug excreted into urine
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
Gmean	Geometric mean
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e antigen
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IP	Investigational Product
IV	Intravenous
IUD	Intrauterine Device
Kel	Elimination rate constant
LLOQ	Lower Limit Of Quantification
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MRT	Mean Residence Time

Abbreviation or special term	Explanation
NCS	Not Clinically Significant
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
PBP	Penicillin-Binding Proteins
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetic
PR	ECG interval measured from the onset of the P wave to the onset of the QRS complex.
PRSP	Penicillin Resistant *Streptococcus pneumonia*
PT	Prothrombin Time
q8h	Every 8 hours
q12h	Every 12 hours
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcB	QT interval corrected for heart rate using Bazett's formula
RBC	Red Blood Cell
RR	The time between corresponding points on 2 consecutive R waves on ECG
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SDV	Source Data Verification
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{½}$	Terminal phase half-life
TCP	Temporal Change Parameter
TEAE	Treatment emergent adverse event
T_{max}	Time to reach maximum (peak) concentration
VISA	Vancomycin-Intermediate Susceptible *Staphylococcus aureus*
VRSA	Vancomycin-Resistant *Staphylococcus aureus*
V_{ss}	Volume of distribution at steady-state
V_z	Volume of distribution during the terminal elimination phase

Abbreviation or special term	Explanation
WBC	White Blood Cell
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Ceftaroline, administered as a prodrug (ceftaroline fosamil), is a synthetic, β- lactam antibiotic in the class of cephalosporins with broad-spectrum activity against contemporary resistant phenotypes such as methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin resistant *Streptococcus pneumoniae* (PRSP), as well as other clinically important gram-positive and gram-negative bacteria. Like most β lactams, ceftaroline inhibits bacterial cell wall biosynthesis in vitro by binding to one or more penicillin-binding proteins (PBPs). Penicillin-binding proteins play an essential role in the biosynthesis of the cell wall and their inhibition is lethal for bacteria. Ceftaroline exhibits unique properties that distinguish it from other β-lactams due to its high affinity for PBP2a in MRSA, and PBP2x in PRSP that contribute to its potent antibacterial activity against these organisms.

A persistent and growing unmet medical need remains for new antibiotics that provide efficacy with a significant therapeutic advancement compared to the current antibiotic armamentarium. Complicated skin and skin structure infections (cSSSI) that require hospitalisation or medical attention is increasing in incidence and, despite advances in medical care and antimicrobial therapy, community-acquired bacterial pneumonia (CABP) remains an important cause of mortality and hospitalisation. New antimicrobials with enhanced spectrum of activity are needed for such serious infections, especially given the rising incidence of highly resistant and highly virulent pathogens such as MRSA, vancomycin-intermediate susceptible *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA), and multidrug-resistant *Streptococcus pneumoniae*.

1.1.1 Clinical Experience

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

The clinical development program for ceftaroline fosamil is comprised of 17 clinical studies, including two Phase 3 cSSSI and two Phase 3 CABP safety and efficacy trials. Approximately 1700 subjects have received ceftaroline as a part of this program. At the recommended dosing regimen of 600 mg administered as a 60-minute IV infusion q12h for 5 to 14 days for treatment of cSSSI and 5 to 7 days for treatment of CABP, ceftaroline fosamil was well tolerated and demonstrated a favourable safety profile that was compatible with treatment of cSSSI and CABP and known cephalosporin class effects. A reduced dose of 400 mg infused over 1 hour q12h is recommended for subjects with moderate renal impairment, defined as a creatinine clearance (CrCl) of 30 mL/min < CrCl ≤ 50 mL/min.
The incidences of treatment emergent adverse events (TEAEs) experienced by subjects receiving ceftaroline fosamil were similar compared with those experienced by subjects receiving comparator therapies. The majority of the TEAEs experienced were mild or

moderate in severity and were assessed as unrelated to ceftaroline fosamil administration. Furthermore, the incidences of death, 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 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. Two seizures were observed in subjects who received ceftaroline fosamil, both occurred more than two days after completion of ceftaroline fosamil therapy. Cephalosporins are known to be associated with positive direct Coombs' test results. The rates of seroconversion from a negative to a positive direct Coombs' test were higher in the ceftaroline group compared with the comparator groups; however no subject was identified with clinical findings or laboratory results that were consistent with haemolytic anaemia. The incidence of potential antibiotic-associated diarrhoea (which can occur with most antibiotics) was low and similar in subjects who received ceftaroline fosamil compared with comparator therapies and resulted in similar numbers of subjects prematurely discontinued from study drug or from the study due to TEAEs of diarrhoea in both treatment groups. Confirmed cases of *C difficile*-associated diarrhoea were rare in both treatment groups.

At the clinical dosages studied (600 mg or 400 mg administered as a 60-minute IV infusion q12h) 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.

Doses of ceftaroline fosamil higher than those studied in the Phase 3 program (eg, single doses up to 2000 mg and multiple doses up to 1800 mg/day [either q12h or q8h]) have been studied in a Phase 1 study (P903-20) and in a Phase 1 ceftaroline fosamil/avibactam study (CXL-PK-01) .The safety of these higher doses of ceftaroline fosamil was consistent with that observed at the 600 mg q12h dose used in the Phase 2 and Phase 3 cSSSI and CABP studies.

1.1.2 Pharmacokinetics of ceftaroline in healthy subjects

Single and multiple dose studies demonstrated that ceftaroline fosamil (prodrug) is rapidly converted in plasma to active ceftaroline following IV infusion. C_{max} and AUC values for ceftaroline increased approximately in proportion to increases in dose within the dose range of 50 to 1000 mg, and no accumulation of ceftaroline fosamil or active ceftaroline was observed with either q12h or every 24 hours multiple-dose regimens. The time of maximum plasma concentrations for ceftaroline generally occurred near the end of the infusion, and the terminal elimination half life ($T_{½}$) of ceftaroline was typically in the range of 2 to 3 hours over the dose range studied (mean of 2.54 ± 0.29 hours in healthy adult subjects with normal renal function across studies). A significant percentage of the ceftaroline fosamil dose was excreted in the urine as ceftaroline (approximately 40% - 70%). Additionally, ceftaroline renal clearance was generally independent of dose and approximately equal to or less than predicted glomerular filtration rate. The plasma protein binding of ceftaroline in vitro was generally low (average

of 20% ± 6.1% bound in Study P0903-P-003) and concentration independent in human plasma over the clinically relevant concentration range (1 to 50μg/mL). These data indicate that interaction of ceftaroline with drugs that are highly bound to plasma proteins is unlikely. Ceftaroline is not a major inhibitor or inducer of major CYP isoenzymes, and therefore is not expected to inhibit or induce the clearance of drugs that are metabolised by these metabolic pathways in a clinically relevant manner.

Ceftaroline is further metabolized by hydrolysis of the β-lactam ring to yield a metabolite, ceftaroline M-1, which lacks antimicrobial activity. Transformation of ceftaroline to ceftaroline M-1 appears to occur independently of cytochrome P450 metabolism.

The safety, tolerability, and PK of ceftaroline following higher single doses of Ceftaroline fosamil, or more frequent dosing administration in multiple dose regimens, were also evaluated. Ceftaroline Cmax and AUC increased approximately in proportion to dose from 1500 to 2000 mg. Following multiple doses of 600 mg ceftaroline fosamil q8h for 10 days, accumulation ratios for ceftaroline (based on AUC) ranged from 1.07 to 1.34 suggesting that no appreciable accumulation of ceftaroline occurs in a q8h dosing regimen.

A Phase 1 study (CXL-PK-01) in healthy subjects was also conducted with 600 mg ceftaroline fosamil administered in combination with the beta-lactamase inhibitor avibactam q8h for 10 days The PK parameters for ceftaroline were similar when ceftaroline fosamil was administered alone and in combination with avibactam in a 600 mg q8h regimen.

For more information about higher doses studies please refer to the investigator's brochure.

1.2 Rationale for conducting this study

The present study is designed to generate pharmacokinetic data of ceftaroline, ceftaroline fosamil, and the ceftaroline metabolite (ceftaroline M-1) for the regulatory requirements in the Chinese population.

1.3 Benefit/risk and ethical assessment

This study will not provide any direct medical benefits to volunteers who participate.

Volunteers will be monitored under supervision in a clinical pharmacology unit (CPU), where management of any adverse events can take place. The dose chosen has been well tolerated in other populations that have been studied.

The Investigator's Brochure for ceftaroline contains the information supporting the overall risk/benefit assessment of the test product and is available as a reference. It contains a summary of all relevant pharmaceutical, non-clinical and clinical findings with ceftaroline.

In the pooled Phase 3 studies for cSSSI and CABP, the incidences of TEAEs were similar in ceftaroline and comparator groups (45.7% vs 46.7%, respectively). The most common TEAE System Organ Class (SOC) in the ceftaroline and comparator treatment groups was Gastrointestinal Disorders (13.3% vs 11.1%, respectively). No individual TEAEs occurred in

5% or more of subjects in the pooled Phase 3 subjects. The most common TEAEs in the ceftaroline group were diarrhoea, headache, nausea, insomnia, constipation, and vomiting. The most common TEAEs in the comparator group were pruritus, nausea, diarrhoea, headache, insomnia, and hypokalemia. The incidences of individual TEAEs were similar in the two treatment groups.

Regarding other adverse events reported less frequently refers to the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1 Primary objective

- The primary objective is to characterize the pharmacokinetics of ceftaroline in healthy Chinese volunteers following single and multiple administration of 600 mg ceftaroline fosamil as 60-minute IV infusion every 12 hours (q12h) and as 120-minute intravenous infusion every 8 hours (q8h).

2.2 Secondary objectives

- To evaluate the safety and tolerability of ceftaroline in healthy Chinese healthy volunteers following single and multiple administration of 600 mg ceftaroline fosamil as 60-minute IV infusion q12h and as 120-minute intravenous infusion q8h.

- To characterize the pharmacokinetics of ceftaroline fosamil and the ceftaroline metabolite (ceftaroline M-1) in healthy Chinese volunteers following single and multiple administration of 600 mg ceftaroline fosamil as 60-minute IV infusion q12h and as 120-minute intravenous infusion q8h.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol 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 centre and open label study, to assess the PK and safety of ceftaroline following single and multiple administration of 600 mg ceftaroline fosamil as 60-minute IV infusion q12h and as 120-minute intravenous infusion q8h in healthy male and female Chinese volunteers. Approximately 24 healthy volunteers will be entered into two groups to obtain at least 10 evaluable subjects for each group. An evaluable subject is defined as a volunteer completing all study procedures from the screening period to the final blood sampling time point for plasma levels of ceftaroline on Day 10 (Group I) or Day 9 (Group II) .

The timing of study assessments is outlined in the Study Plan (Table 1). Subjects will undergo screening assessments during the 21-day period preceding administration of the first

dose of study drug on Day 1. Subjects will report to the study unit the day before administration of the first dose of study drug (Day -1) and will remain confined there until completion of study procedures on Day 10 (Group I) or Day 9 (Group II). In addition, subjects will return to the CPU for a follow up visit approximately 5-10 days after the discharge from the CPU. Each subject's participation, including the screening period, will take 41 days (Group I) or 40 days (Group II).

This study will be conducted in two groups of healthy volunteers. The groups will be recruited sequentially.

Group I: 12 healthy volunteers will receive a single 600 mg ceftaroline fosamil as 60-minute IV infusion in the morning on Day 1 and 8. On Days 3 -7 volunteers will receive 600 mg ceftaroline fosamil as 60-minute IV infusion q12h. On day 2, the volunteers will not receive drug, but plasma and urine PK sample will be obtained.

Group II: 12 healthy volunteers will receive a single 600mg ceftaroline fosamil as 120-minute IV infusion in the morning on Day 1 and 8. On days 2 -7 volunteers will receive 600mg ceftaroline fosamil as 120-minute IV infusion q8h.

Plasma and urine PK samples will be obtained at the times noted in the PK Plasma and Urine Sampling schedule (Table 2).

Safety assessments including physical examinations, laboratory assessments, 12-lead ECGs, and vital sign measurements will be performed according to the schedule in the Study Plan. If the subject had rash, additional test may be required to understand the immunological disposition of subjects such as HLA typing etc. (Table 1).

Principal investigator and AstraZeneca appropriate personnel will review the safety data after Group I last subject out, to determine if the next sequential cohort (Group II) may be enrolled as planned. The safety data (including all adverse events and laboratory data collected during the Group I drug administration phase) will be summarized and made available to the ethics committee for endorsement prior to the start of the enrolment of subjects in Group II.

Table 1 Study Plan

Assessment	Visit 1	Visit 2										Visit 3
	Screening	Study Day										Follow up
	Day –21 to -2	-1	1	2	3	4	5	6	7	8	9	10	5-10 days after discharge
Informed consent	X												
Demographics	X												
Inclusion/exclusion criteria	X	X											
Medical/surgical history	X												
Group I													
Complete physical exam	X	X										X	
Brief physical exam			X	X	X	X	X	X	X	X	X		X
12-lead ECG	X	X	X		X		X		X			X	X
Vital signs (BP, pulse, oral temp)	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety labs(Clinical chemistry, Haematology,Urinalysis)	X	X			X				X			X	X
Safety labs(Coagulation)		X										X	X
Safety labs(Coombs)		X										X	X
Pregnancy test	X	X										X	X
Alcohol breath test	X	X											
Drugs abuse screen	X	X											
Virology screen	X												
Ceftaroline fosamil dose[1]			X		X	X	X	X	X	X			

Assessment	**Visit 1** **Screening** **Day –21 to -2**	**Visit 2** **Study Day** **-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Visit 3** **Follow up** **5-10 days after discharge**
PK plasma samples[2]			X	X	X	X	X	X	X	X	X	X	
PK urine samples[2]			X	X	X					X	X	X	
Confinement to CPU		◄	———	———	———	———	———	———	———	———	———	———	
AE monitoring			◄	———	———	———	———	———	———	———	———	———	►
SAE monitoring	◄	———	———	———	———	———	———	———	———	———	———	———	►
Group II	Screening	-1	1	2	3	4	5	6	7	8	9	10	Follow up
Complete physical exam	X	X									X		
Brief physical exam			X	X	X	X	X	X	X	X			X
12-lead ECG	X	X	X		X		X		X		X		X
Vital signs (BP, pulse, oral temp)	X	X	X	X	X	X	X	X	X	X	X		X
Safety labs(Clinical chemistry, Haematology,Urinalysis)	X	X			X			X			X		X
Safety labs(Coagulation)		X					X				X		X
Safety labs(Coombs)		X											X
Pregnancy test	X	X									X		X
Alcohol breath test	X	X											
Drugs abuse screen	X	X											
Virology screen	X												

Assessment	Visit 1	Visit 2										Visit 3
	Screening	Study Day										Follow up
	Day –21 to -2	-1	1	2	3	4	5	6	7	8	9	10	5-10 days after discharge
Ceftaroline fosamil dose[1]			X	X	X	X	X	X	X	X			
PK plasma samples[2]			X	X	X	X	X	X	X	X	X		
PK urine samples[2]			X	X						X	X		
Confinement to CPU		◄	———	———	———	———	———	———	———	———	———	►	
AE monitoring			◄	———	———	———	———	———	———	———	———	———	►
SAE monitoring	◄	———	———	———	———	———	———	———	———	———	———	———	►

[1] The subjects of Group I will receive a single 600 mg dose of ceftaroline fosamil as 60-minute IV infusion in the morning on Day 1 and 8. On Days 3 through 7, subjects will receive 600 mg ceftaroline fosamil q12h. Each IV infusion will be administered as a 60-minute infusion. The subjects of Group II will receive a single 600 mg dose of ceftaroline fosamil as 120-minute IV infusion in the morning on Days 1 and 8. On Days 2 through 7, subjects will receive 600 mg ceftaroline fosamil q8h. Each IV infusion will be administered as a 120-minute infusion

[2] See Table 2 for PK Plasma and Urine Sampling Schedule.

If the subject had rash, additional test may be required to understand the immunological disposition of subjects such as HLA typing etc.

Table 2 PK Plasma and Urine Sampling Schedule

Sample	Schedule[1]
Group I	
Plasma samples	Four (4) mL samples for the determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 plasma concentrations will be obtained at the following times: Day 1: Pre-dose, 20 min, 40 min, 55 min (within 5 minutes before the end of study infusion), 65 min (within 5 minutes after the end of study infusion), 75 min, 1.5 hr, 2 hr, 3 hr ,4 hr, 6hr , 8 hr, 12 hr, 18 hr, 24 hr, 36 hr and 48 hr after the start of infusion of the study drug. Days 3 through 7: Within 10 minutes before the start of the morning infusion (pre-dose sample on Day 3 is the same plasma sample of the 48 hr plasma sample following the single dose on Day 1) Day 8: Pre-dose, 20 min, 40 min, 55 min (within 5 minutes before the end of study infusion), 65 min (within 5 minutes after the end of study infusion), 75 min, 1.5 hr, 2 hr, 3 hr,4 hr, 6hr , 8 hr, 12 hr, 18 hr, 24 hr, 36 hr and 48 hr after the start of infusion of the study drug.
Urine samples	Days 1 and 8: Urine collected pre-dose (within 30 min prior to dosing) and during the 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, and 24-48 hour intervals after start of the study drug infusion
Group II	

Sample	Schedule[1]
plasma samples	Four (4) mL samples for the determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 plasma concentrations will be obtained at the following times: Day 1: Pre-dose, 60 min, 90 min, 115 min (within 5 minutes before the end of study infusion), 125 min (within 5 minutes after the end of study infusion), 2 hr15min, 2.5hr, 3 hr ,4 hr, 6hr, 8 hr, 12 hr, 18 hr, 24 hr after the start of infusion of the study drug. Days 2 through 7: Within 10 minutes before the start of the morning infusion (pre-dose sample on Day 2 is the same plasma sample of the 24 hr plasma sample following the single dose on Day 1) Day 8: Pre-dose, 60 min, 90 min, 115 min (within 5 minutes before the end of study infusion), 125 min (within 5 minutes after the end of study infusion), 2 hr15min, 2.5hr, 3 hr ,4 hr, 6hr, 8 hr,12hr,18hr,24hr after the start of infusion of the study drug.
Urine samples	Days 1 and 8: Urine collected pre-dose (within 30 min prior to dosing) and during the 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 and 12-24 intervals after start of the study drug infusion

[1] Pre-dose blood samples on Day 1 will be taken during the 30-minute period preceding the start of infusion; Pre-dose blood samples on the other pre-dose sampling days will be taken during the 10-minute period preceding the start of infusion; Other plasma samples will be taken as close to the nominal sampling times as possible.

3.2 Rationale for study design, doses and control groups

The design of this study is based on pharmacokinetic studies of ceftaroline conducted throughout the development program.

Healthy volunteers are being chosen to minimize the effect of concurrent illness or medication on the pharmacokinetic assessments.

The dose levels chosen are expected to give adequate characterization of the pharmacokinetic profile around the expected exposures to ceftaroline from the anticipated therapeutic dose.

Single and multiple dosing of ceftaroline will be employed to assess:

1. the safety and tolerability after a single and multiple dose administration of ceftaroline fosamil at steady-state and

2. to characterize the pharmacokinetics of ceftaroline, ceftaroline fosamil and ceftaroline M-1 after a single and multiples dose administration of ceftaroline fosamil at steady-state

4. SUBJECT SELECTION CRITERIA

Investigator(s) should keep a record, the subject-screening log, of subjects who entered pre-study screening.

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

4.1 Inclusion criteria

For inclusion in the study volunteers must fulfil all of the following criteria:

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

2. Are healthy male or female Chinese volunteers aged between 18 and 45 inclusive. Female subjects must meet one of the following conditions:

   - Have been surgically sterilized (hysterectomy or tubal-ligation) at least 12 months prior to screening

- Are postmenopausal having had no regular menstrual bleeding for at least one (1) year prior to screening. Menopause will be confirmed by a plasma follicle stimulating hormone (FSH) level of > 35 IU/mL at screening

- Are willing to use two of the following effective means of non-hormonal contraception, one of which must be a barrier method (vasectomized partner, condom, intrauterine device (IUD), diaphragm, cervical cap with spermicide) for the duration of the study including the follow up period;

3. Have a Body Mass Index (BMI) between (and including) 19 and 24 kg/m^2 and weigh at least 50 kg.

   BMI =Weight (kg) / Height^2 (m^2)

4. Be willing to communicate with the investigator and comply with all study procedures

4.2 Exclusion criteria

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

1. Clinically significant abnormal physical examination, laboratory values, 12-lead ECG or vital signs.

2. CL_{CR} <80 mL/min as calculated by the Cockroft Gault equation

$$\textit{Males: } CL_{CR} = \frac{(140\text{-age}) \times (\text{kg body weight})}{(72 \times \text{mg/dl serum creatinine})}$$

$$\textit{Females: } CLCR = \frac{(140\text{-age}) \times (\text{kg body weight}) \times 0.85}{(72 \times \text{mg/dl serum creatinine})}$$

   Where age is expressed in years, weight in kg, and serum creatinine in mg/dl

3. History of neurological, haematological, psychiatric, gastrointestinal, hepatic or renal disease or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs as determined by the investigator;

4. History of any hypersensitivity or allergic reaction to any β-lactam antimicrobial

5. Symptoms of any clinically significant illness within 2 weeks of screening

6. Blood donation with 3 months of screening

7. Use of any over the counter preparations including herbal preparations and vitamins in the 2 weeks prior to the first dose.

8. Use of prescription medication for acute or chronic medical conditions within 4 weeks prior to the first dose of study medication. Use of hormone replacement therapy for female volunteers is permitted as long as there has been no change in the dosing regimen for at least 3 months prior to screening

9. Current and/or past history of alcohol abuse within the past year or a positive breath test for alcohol abuse

10. Current and/or past history of drugs abuse within the past year or a positive drug abuse screen, e. g. amphetamines, barbiturates, benzodiazepines, cocaine and/or metabolites, methadone, methamphetamine including ecstasy, opiates, phencyclidine (PCP),and tetrahydrocannabinol (THC).

11. Use of tobacco or history of use of tobacco(> 5 tobacco/week) or nicotine-containing products in the 3 months prior to screening

12. Positive results of pregnancy test or currently lactating

13. Positive results of human immunodeficiency virus , Hepatitis B surface antigen or Hepatitis C antibody testing

14. A suspected/manifested infection according to World Health Organization risk categories 2, 3 and 4. See Appendix D.

15. Use of any other investigational compound or participation in another clinical trial within 2 months prior to Visit 2

16. Consumption of alcohol-, caffeine-, xanthine--containing foods or beverages within 48 hours preceding study drug administration

17. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)

18. Volunteers, who, in the opinion of the investigator, should not participate in this study

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Volunteers have the following restrictions unless approved by the investigator and sponsor:

1. Refrain from consumption of alcohol or xanthine-containing foods or beverages (such as caffeine) within 48 hours preceding study drug infusion until after the final medical examination at the study follow-up.

2. Refrain from strenuous exercise from 48 hours prior to Visit 2 until after the final medical examination at the study follow-up.

3. Refrain from the use of over-the-counter preparations including herbal remedies such as Cordyceps sinensis, dan shen, feverfew, Ganoderma lucidum, ephedra, echinacea, St. John's Wort, and garlic, [aged extract taken on an ongoing basis], ginseng, ginkgo, and vitamin preparations from 2 weeks prior to Visit 2 until after the final medical examination at the study follow-up.

4. Refrain from the use of prescribed medications from 4 weeks prior to Visit 2 until after the final medical examination at the study follow-up.

5. Refrain from the use of tobacco or other nicotine-containing products from Screening Period until after the final medical examination at the study follow-up.

6. Refrain from donating blood from the Screening Period t until 56 days after their last dose of ceftaroline

5.2 Subject enrolment

The Principal Investigator will:

1 Obtain signed informed consent from the potential subject before any study specific procedures are performed

2 Assign potential subject a unique enrolment number, beginning with 'E'

3 Determine subject eligibility. See Sections 4.1 and 4.2

4 After Informed consent is obtained and the screening evaluation is completed, the eligible subjects will be assigned a randomization code. Randomization codes will be assigned consecutively.

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

5.3 Procedures for handling subjects incorrectly enrolled

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

Where subjects that do not meet the selection criteria are enrolled in error or incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the subject from treatment.

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

5.4 Blinding and procedures for unblinding the study – Not Applicable

5.5 Treatments

5.5.1 Identity of investigational product(s)

Ceftaroline fosamil for injection is supplied as 600 mg of the prodrug of ceftaroline, a sterile pale yellowish-white to light yellow crystalline powder in a single-dose, clear glass 20 mL vial. An excipient, L-arginine (approximately 660 mg L-arginine/g of ceftaroline prodrug), is added as an alkalizing agent to control pH of the constituted solution to pH 4.8 to 6.2. The product is limited to investigational use only. Please refer to the current IB for additional information.

Table 3 Identity of Investigational Product

Investigational product	Dosage form and strength	Manufacturer
Ceftaroline fosamil	Ceftaroline fosamil powder for concentrate for solution for infusion, 600 mg	

5.5.2 Doses and treatment regimens

Group I: 12 healthy volunteers will receive a single 600 mg IV infusion of ceftaroline fosamil in the morning on Days 1 and 8. On Days 3 -7 the volunteers will receive 600 mg ceftaroline fosamil IV infusion q12h. Each IV infusion will be administered as a 60-min IV infusion.

Group II: 12 healthy volunteers will receive a single 600mg ceftaroline fosamil as 120-minute IV infusion in the morning on Day 1 and 8. On day 2 -7 the volunteers will receive 600mg ceftaroline fosamil as 120-minute IV infusion q8h.

5.5.3 Labelling

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

The vial labels will contain information including:

- Study Code
- Drug name, Dosage form, Dosage quantity
- Route of administration
- Sponsor name
- Space to complete the following:
    1. Enrolment Code
    2. Date of Administration

A tear-off dispensing label will be used for infusion bag; the tear-off portion of the label will be affixed to patient record forms. The label will contain information including:

- Study Code
- Drug name, Dosage form, Dosage quantity
- Route of administration
- Storage conditions
- Sponsor name
- Space to complete the following:
    1. Enrolment Code
    2. Date of Administration

3. Time and date of Preparation

5.5.4 Storage

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

5.5.5 Direction for administration of ceftaroline fosamil

Vials of ceftaroline for injection are constituted with 20.0 mL of sterile water for injection. The amount of the resulting solution required for each dose is transferred to a sodium chloride 0.9% infusion bag. Refer to the Study Handling Instructions for detailed information on study drug preparation.

5.6 Concomitant and post-study treatment(s)

No concomitant medication or therapy will be allowed unless approved by the investigator and sponsor. The volunteers must be instructed that no additional medication will be allowed without the prior consent of the investigator.

Any medication, which is considered necessary for the volunteer's safety and well being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the electronic case report form (eCRF).

5.7 Treatment compliance

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

Compliance will be assured by supervised administration of the investigational product by the investigator and/or his or her designee.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in this study protocol.

The study personnel will account for all study drugs dispensed to and returned from the subject.

The investigator (or delegate) is responsible for maintaining drug accountability records for study drugs. Drug accountability for this study will be carried out in accordance with standard procedures at the study centre.

All unused drugs will be accounted for and destroyed appropriately by AstraZeneca designated personnel. The study personnel will account for all drugs dispensed. Certificates of delivery, destruction and return must be signed.

5.8 Discontinuation of investigational product

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

- Subject decision. The subject is at any time free to discontinue his/her participation in the study without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol
- Incorrect enrolment i.e., the volunteer does not meet the required inclusion/exclusion criteria for the study
- Volunteer lost to follow-up

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.3.3 and 6.3.4); and all study drugs should be returned by the subject.

If a subject is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study, without prejudice to further treatment (withdrawal of consent), but once dosing has occurred every attempt should be made to continue assessments to ensure the safety of the volunteer. Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.3.3 and 6.3.4) and all study drugs should be returned by the subject.

Volunteers who withdraw from the study due to reasons other than an AE may be replaced at the discretion of the Sponsor and/or investigator. All replacements must be approved by AstraZeneca. Volunteers who are withdrawn from the study by the investigator due to AEs after the start of dosing will not be replaced. If a volunteer withdraws his/her participation in the study, then his/her enrolment code cannot be reused.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRF as specified in the study protocol 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 eCRFs will be archived at the study site.

The study assessments are described in the sections below and the timing of these assessments are detailed in the Study Plan and PK Plasma and Urine Sampling Schedule (Table 1and Table 2).

In order to collect blood samples for pharmacokinetic analysis at the precise scheduled time, other assessments may be initiated prior to or after their scheduled time point to ensure that the pharmacokinetic blood sample is collected on time. If multiple procedures are scheduled at the same time point, safety assessments may need to be initiated early as follows:

- 12-lead ECG recordings
- Vital signs measurement
- Blood/urine sampling for determination of pharmacokinetics of ceftaroline (collected on time)
- Blood sampling for laboratory assessments

The actual time for all assessments will be recorded in the eCRF. Pre-dose assessments, except PK blood samples, may be done up to 30 minutes prior to dosing. Pre-dose blood samples on Day 1 will be taken during the 30-minute period preceding the start of infusion. Pre-dose blood samples **on the other pre-dose sampling days** will be taken during the 10-minute period preceding the start of infusion.

6.2 Data collection and enrolment

Data will only be entered into eCRFs for subjects who are enrolled and receive at least one dose of study medication.

6.3 Safety

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

6.3.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). 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 to include both serious and non-serious AEs.

6.3.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout and follow-up), that fulfils one or more of the following criteria:

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

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from the time study drug is first administered throughout the treatment period and including completion of scheduled study procedures.

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any AEs that are unresolved at time of the final scheduled study assessment are to be 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 subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE:

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a 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 a SAE.

In case seizures, haemolytic anaemia, renal failure and DILI (drug-induced liver injury) occur during the study, irrespective of their seriousness, additional information will be requested and collected by way of targeted follow-up questionnaires in the WBDC (Web Based Data Capture) system or by manual intake forms. Details regarding these questionnaires may be found in Appendix B.

Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the 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 and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and 12-lead ECGs findings should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

NB. Cases where a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix E ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law’, for further instructions.

6.3.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives within one day i.e., immediately **but no later than the end of the next business day** of when he or she becomes aware of it, **and report to the Ethics Committee and Regulatory authority based on local drug administration laws and regulations.**

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 i.e., immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times given in the Study Plan (Table 1). The date of collection will be recorded in the appropriate eCRF.

If any of the tests performed on the samples taken after investigational product administration show clinically significantly abnormal results as judged by the investigator, new blood samples will be obtained and tests repeated until the results return to baseline or the cause is assessed. The investigator will provide an evaluation of the clinical importance of the deviation. The development of any clinically relevant deterioration in any laboratory parameter may constitute an AE if it leads to discontinuation of the study drug or if it fulfils the criteria of seriousness. The investigator will record on the laboratory report whether the abnormality is Clinically Significant (CS) or Not Clinically Significant (NCS).

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

Table 4 Clinical laboratory tests

Haematology	Clinical Chemistry	Urinalysis	Virology (screening only)	Other[1]
Haemoglobin	Magnesium	pH	HBV (HBeAg, HBsAg)	Urine pregnancy test for women of child bearing potential
Hematocrit	Bicarbonate	Specific gravity	HCV	
Red blood cell count (RBC)	Sodium	Glucose	HIV	
WBC	Potassium	Ketone		
WBC differential (percentages and absolutes)	Phosphorus	Protein		
Mean corpuscular volume	Chloride	Bilirubin		
Mean corpuscular haemoglobin	Calcium	RBC		
Mean corpuscular haemoglobin concentration	Alkaline phosphates	WBC		
Platelet count	Gamma-glutamyl transferase	Crystals		
Prothrombin time (PT)	ALT	Casts		
PT/international normalized ratio (INR)	AST	Microscopic examination of the sediment if positive for blood or protein.		
Partial thromboplastin time	Lactic dehydrogenase			
Direct Coombs' test	Total bilirubin			
	Total cholesterol			
	Triglycerides			
	Glucose			
	Total protein			
	Albumin			
	Creatine kinase			
	Serum creatinine			
	Urea nitrogen			
	Uric Acid			

[1] If the subject had rash, additional test may be required to understand the immunological disposition of subjects such as HLA typing etc.

For blood volume see Section 7.1

6.3.6 Physical examination

Physical examinations will be conducted according to the schedule outlined in the Study Plan (Table 1).

6.3.6.1 Complete physical examination

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears and throat), lymph nodes, thyroid, musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen, and neurological systems.

Complete physical examination data to be recorded in the eCRF will include:

- Normal
- Abnormal with a description of any abnormalities
- Same as previous

6.3.6.2 Brief physical examination

The brief physical examination will include an assessment of the following items: general appearance, abdomen, lungs, and the cardiovascular system.

Brief physical examination data to be recorded in the eCRF will include:

- Normal
- Abnormal with a description of any abnormalities
- Same as previous

6.3.6.3 Height and weight measurements

Height (m) and weight (kg) will be measured without shoes. BMI will be calculated as weight (kg)/height^2 (m^2) and will be recorded in the eCRF.

6.3.7 12-lead ECG

12-lead ECGs will be obtained at the time presented in the Study Plan (Table 1) after the subject has been lying down for 10 minutes in each case.

ECG Schedule:

Screening Day: Obtain one 12-lead ECGs at least 1 minute duration, within a 15minute period.

Group I:

Day-1: Three separated by at least 1 minute, within a 15minute period.

Day 1, 3, 5, 7: Obtain one 12-lead ECGs within 60 minutes of the end of infusion 1.

Day 10 and Followup Day: Obtain one 12-lead ECGs at least 1 minute duration.

Group II:

Day-1: Three separated by at least 1 minute, within a 15minute period.

Day 1, 3, 5, 7: Obtain one 12-lead ECGs within 60 minutes of the end of infusion 1.

Day 9 and Followup Day: Obtain one 12-lead ECGs at least 1 minute duration.

In order to collect blood samples for pharmacokinetic analysis at the precise scheduled time, 12-lead ECG may be initiated prior to their scheduled time point to ensure that the pharmacokinetic blood sample is collected on time. The precise time for 12-lead ECG recordings will be recorded in the eCRF. See section 6.1.

All ECGs will be documented by recording date, time of collection, heart rate, PR, RR, QRS, QT, QTcF and QTcB Intervals (the QT correction factor will be based on the Fridericia's and Bazett's formula) from the 12-lead ECG.

The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. The reason for the abnormality will be recorded in the eCRF. These ECGs will be documented in the eCRF by recording date, time, heart rate, and overall assessment as normal and abnormal.

All 12-lead ECGs will be recorded and evaluated by the investigator. If indicated additional 12-lead ECG assessments can be made at the discretion of the investigator. These assessments should be entered as an unscheduled assessment in the appropriate eCRF.

6.3.8 Vital signs

Vital sign measurement will be taken at the times indicated in Study Plan (Table 1).

In order to collect blood samples for pharmacokinetic analysis at the precise scheduled time, vital signs measurement may be initiated prior to their scheduled time point to ensure that the

pharmacokinetic blood sample is collected on time.The precise time for vital signs recordings will be recorded in the eCRF. See section 6.1.

6.3.8.1 Pulse and blood pressure

For timing of individual measurements refer to the Study Plan (Table 1)

Group I: Screening day, Day-1, **Day 2**, Day 9, Day 10 and Followup day: blood pressure and pulse will be measured once a day.

On day 1 to Day 8**(except Day 2)**: At pre, 2, 3, 4 and 6 hours after the end of infusion 1 blood pressure and pulse will be measured. Blood pressure and heart rate will be measured as per site procedures with an appropriate cuff size. Volunteers will be sitting 5 minutes before assessments. As much as possible, blood pressure will be measured using the same arm per volunteer throughout the study.

Group II: Screening day, Day-1, Day 9 and Followup day: blood pressure and pulse will be measured once a day.

On Day 1 to Day 8: At pre and 2 hours after the end of infusion 1 blood pressure and pulse will be measured. Blood pressure and heart rate will be measured as per site procedures with an appropriate cuff size. Volunteers will be sitting 5 minutes before assessments. As much as possible, blood pressure will be measured using the same arm per volunteer throughout the study.

6.3.8.2 Body temperature

Body temperature will be measured in degrees Celsius at the times indicated in the Study Plan (Table 1). Measure the temperature in the morning and again in the afternoon. The highest daily temperature will be recorded.

6.3.9 Safety Data Review

Principal investigator and AstraZeneca appropriate personnel will review the safety data after Group I last subject out, to determine if the next sequential cohort (Group II) may be enrolled as planned. The safety data (including all adverse events and laboratory data collected during the Group I drug administration phase) will be summarized and made available to the ethics committee for endorsement prior to the start of the enrolment of subjects in Group II.

6.4 Patient reported outcomes (PRO) – Not applicable

6.5 Pharmacokinetics

6.5.1 Pharmacokinetic plasma samples

6.5.1.1 Collection of pharmacokinetic blood samples

Blood samples (4 mL) for determination of ceftaroline fosamil, ceftaroline and ceftaroline M-1 concentrations in plasma will be taken at the times presented in the PK Plasma and Urine Sampling Schedule (Table 2). Where more than one assessment occurs at any time-point the PK sample will be given priority and taken at the correct protocol-specified time (Section 6.1). Individual venipunctures for each time point may be performed or an in-dwelling catheter may be used. If the site chooses to use an in-dwelling catheter, the first 1 mL of blood will be discarded and the catheter flushed with saline following the sampling. Heparin may not be used to flush the catheter.

The following sample collection procedure must be followed:

1. Collect 4-mL blood into one chilled Sodium flouride/Potassium Oxalate tube. Invert the tube gently 10 times to mix the blood and anticoagulant.
2. Centrifuge the tube immediately (within 15 minutes from the time blood is drawn) at approximately 1500 times gravity for 15 minutes in a refrigerated centrifuge (4°C).
3. Immediately transfer the entire volume of plasma from the Sodium flouride/Potassium Oxalate tube into the four prepared and chilled cryotubes; place approximately 0.5 mL plasma in each tube.
4. Freezer (-70°C or below) compatible labels must be applied to the intended PK sample and the pre-printed information must not be changed. The label affixed must contain the following information:

- Study Number: D3720C00005
- Subject identification number
- Nominal day and Time of collection
- Matrix: Plasma
- Aliquot # (Aliquot 1, Aliquot 2, Aliquot 3, or Aliquot 4)

5. IMMEDIATELY FREEZE all four samples in isopropanol/dry ice bath and store upright at -70°C or below.
6. Record the ACTUAL DATE/TIME that the blood sample was collected in the eCRF.

7. Send two of the frozen samples to the testing laboratory according to the PK Collection and Shipment Instructions Manual. Keep the other frozen sample for backup.

6.5.2 For shipping of PK samples refer to Section 6.5.3 Pharmacokinetic urine samples

6.5.2.1 Collection of pharmacokinetic urine samples

Urine samples for determination of ceftaroline fosamil, ceftaroline and ceftaroline M-1 concentrations will be taken at the times presented in the PK Plasma and Urine Sampling Schedule (Table 2).

The following sample collection procedure must be followed:

1. Each subject will pass all urine into a collection container at the time intervals as specified in the PK Plasma and Urine Sampling Schedule (Table 2).

2. Each void of urine will be pooled into 1 container and refrigerated (4 ± 2°C) for the duration of each collection period. Refrigerated (4 ± 2°C) compatible labels must be applied to these containers. The label affixed must contain the following information:

- Study Number: D3720C00005
- Subject identification number
- Start Date and Start Time of collection interval
- End Date and End Time of collection interval
- Volume
- pH (by pH test paper)
- Matrix: Urine

3. Following the completion of the urine collection for a given interval, the sample will be thoroughly mixed; the **pH and VOLUME, along with the End Date and End Time of the collection interval** will be determined and recorded on the label and in the eCRF.

4. At the completion of each collection interval, extract and retain two 2 mL aliquots inseparate universal sterile containers.

5. Freezer (-70°C or below) compatible labels must be applied to these intended PK urine samples and the pre-printed information must not be changed. The label affixed must contain the following information:

- Study Number: D3720C00005
- Subject identification number
- Nominal day
- Scheduled collection interval

6. Matrix: UrineImmediately freeze sample in isopropanol/dry ice bath and store in freezer at -70°C or below. The sample must be stored upright, and kept frozen at this temperature before, during and after transport to the designated laboratory.

7. Send one of the frozen urine samples to the testing laboratory according to the PK Collection and Shipment Instructions Manual. Keep the other sample frozen for backup.

For shipping of PK samples refer to Section 6.5.3.

6.5.3 Shipping of pharmacokinetic samples

All PK plasma and urine samples accompanied by the specimen shipment logs will be shipped via an agreed-upon overnight courier. The frozen samples must be packed securely to avoid breakage during transit, and contact with other tubes, which would jeopardise the legibility of identifying labels. The samples should be double bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 96 hours to allow for delays in shipment. The samples from each healthy volunteer will be placed in separate bags and labelled as instructed in Section 6.5.1and 6.5.2. All applicable shipping regulations must be followed. Documentation sufficient to identify each sample must be included in the shipment. This documentation must also note any samples not processed according to the protocol's specifications.

Ship samples on Mondays – Wednesdays. Do not ship within three days before a legal holiday.

The primary contact at AstraZeneca and the laboratory must be notified at the time the samples are shipped. AstraZeneca will provide the necessary shipping and contact information regarding the bioanalytical laboratory prior to the start of the study.

The primary contact at AstraZeneca will be:

Li Liang
AstraZeneca R & D Wilmington
Regulatory Bioanalysis, Global DMPK-IM
OW1-321
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437
Tel: +01 302 885 5699
Fax: +01 302 886 5345
Email: li.liang@astrazeneca.com

6.5.4 Determination of drug concentration

Samples for determination of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 concentration in human plasma will be analysed by a Bioanalytical Laboratory to be determined on behalf of AstraZeneca. Full details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

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

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 5 Volume of Blood to be drawn from Each Subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	4	6	24
	Haematology	2	6	12
	Coagulation (Group I)	2	3	6
	Coagulation (Group II)	2	4	8
	Virology	4	1	4
	Coombs (Group I)	5	3	15
	Coombs (Group II)		2	10
Pharmacokinetic[1]		4 ～5[1]	38 33	～190(Group I) ～165(Group II)
Total		～22	57 52	～251(Group I) ～223 (Group II)

[1]PK sample volume includes 1 ml per sample to be discarded when line is flushed

7.2 Handling, storage and destruction of biological samples

7.2.1 Pharmacokinetic samples

Samples will be disposed of after the clinical study report has been finalised.

7.3 Labelling and shipment of biological samples

The Principal 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 'IATA 6.2 Guidance Document'.

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

7.4 Chain of custody of biological samples

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

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

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

AstraZeneca 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 biobank 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 laboratory holding the samples is 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/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

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

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable 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 enrolment of any subject into the study. The Ethics Committee should approve all advertising used to recruit subjects for the study.

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

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

The Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions (SUSAR) from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Principal Investigator will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects 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 its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the

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

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

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, 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 subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the investigator(s) or otherstaff at the centre needs information and advice about the study conduct.

9.3.1 Source data

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

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

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

The study is expected to start in Q4, 2011 and to end by Q1, 2012.

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

10. DATA MANAGEMENT BY COGNIZANT DATA MANAGEMENT CENTRE

The Cognizant Data Management Centre (DMC) will perform data management

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 of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the DMC.

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

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

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

Dictionary coding

Medical coding is done using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and AstraZeneca Drug Dictionary. Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. The Medical Coding Team at the Data Management Centre will perform all 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 (if applicable). External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

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

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of pharmacokinetic variables

The PK analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations and the investigator will be instructed to obtain the plasma samples for PK analysis at the indicated times in the PK Plasma and Urine Sampling Schedule (Table 2). For reporting purposes the plasma samples for PK analysis will be considered on time if they meet the following criteria:

- plasma samples for PK analysis taken up to 1.5 hr after the start of infusion of the study drug can be obtained ± 5 minutes relative to the scheduled times
- plasma samples for PK analysis taken up to 2-8 hr after the start of infusion of the study drug can be obtained ± 15 minutes relative to the scheduled times

- Other plasma samples for PK analysis can be obtained ± 1 hour relative to the scheduled times

Plasma and urine concentrations of ceftaroline will be determined for each subject that received ceftaroline using standard non-compartmental methods. Where possible, PK parameters for ceftaroline, ceftaroline fosamil and ceftaroline M-1 will include but not be limited to:

Plasma PK

- Single dose: AUC, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, C_{max}, T_{max}, CL, MRT, T54, V_{ss},V_z, and Kel
- Multiple dose: AUC, $AUC_{(0-\tau)}$, $AUC_{(0-t)}$, $C_{ss,\,max}$, $C_{ss,\,min}$, $C_{ss,\,av}$, T_{max}, CL, MRT, T54, V_{ss}, V_z, $AR_{(Cmax)}$, $AR_{(AUC)}$, Kel, TCP, and DF

Urine PK

- A_e, f_e and CL_R

Where:

- AUC = area under plasma concentration-time curve from zero to infinity;
- $AUC_{(0-\tau)}$ = area under the plasma concentration-time curve from time zero to the end of dosing interval for a repeated dosing regimen; τ will be 12 and 8 hours for Group I and Group II, respectively;
- $AUC_{(0-t)}$ = area under the plasma concentration-time curve from time zero to time of last quatifiable plasma concentration
- C_{max} = maximum (peak) plasma concentration
- $C_{ss,\,max}$ = Maximum (peak) steady state drug concentration in plasma during dosing interval
- $C_{ss,\,min}$ = Minimum (trough) steady state drug concentration in plasma during dosing interval
- $C_{ss,\,av}$ = Average drug concentration in plasma during a dosing interval at steady state
- T_{max} = time to reach maximum (peak) concentration

- CL = Absolute clearance for ceftaroline fosamil and apparent clearance for ceftaroline and ceftaroline M-1
- CL_R = renal clearance
- $T_?$= terminal phase half-life
- V_{ss} = volume of distribution at steady-state (only calculable for ceftaroline fosamil)
- V_z = volume of distribution during the terminal elimination phase
- A_e = cumulative amount of unchanged drug excreted into the urine
- f_e = Fraction of intravenously administered drug excreted into urine
- $AR_{(Cmax)}$ = accumulation ratio calculated from C_{max}
- AR(AUC) = accumulation ratio calculated from $AUC_{(0-\tau)}$
- MRT = mean residence time
- TCP = temporal change parameter, which is the ratio of $AUC_{(0-\tau)}$ of the last dose over the AUC of the first dose.
- DF = Degree of fluctuation, which is 100% ?($C_{ss,max} - C_{ss,min}$)/$C_{ss,av}$
- Kel = Terminal phase elimination constant

Additional parameters may be calculated as deemed appropriate (e.g., area under the first moment curve, % AUC extrapolated, etc.).

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory, vital signs, and ECG data will be performed for identification of OAEs.

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

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

Subjects will be classified as valid or non-valid for safety and pharmacokinetic analyses and finalised before database lock.

12.1.1 Pharmacokinetic analysis set

Any subject who provides at least one plasma concentration data with no important protocol deviations will be classified as valid for the pharmacokinetic analysis.

A strategy for dealing with PK data affected by deviations will be agreed by the study team physician, pharmacokineticist and statistician prior to clean file and database lock.

12.1.2 Safety analysis set

All subjects who have received study drug and for whom post-dose information is available will be evaluated as valid for safety.

12.2 Methods of statistical analyses

All statistical analyses will be carried out under the direction of the Biostatistics Group, AstraZeneca.

Safety, tolerability and PK data will be listed and summarised **by treatment group** using descriptive statistics. Graphical representations of data will be presented as is deemed appropriate. No formal hypotheses testing will be conducted in this study.

12.2.1 Pharmacokinetic data

PK data of Ceftroline, Ceftaroline Fosamil and Ceftaroline M-1 will be analysed separately.

Plasma concentrations at each sampling time point will be summarised **by treatment group** according to dosing period by the following summary statistics:

- Geometric Mean (Gmean) (calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)

- CV (calculated as $100\sqrt{[\exp(s^2)-1]}$, where s is the standard deviation(SD) of the data on a logarithmic scale)
- Gmean ± SD (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data
- SD calculated using untransformed data
- Minimum
- Maximum
- Number of observations
- Number of observations ≥ LLOQ

Geometric mean plasma concentrations against protocol time will be shown in one graph at single and multiple dose periods using the vertical axis in both linear and log scales, respectively. Note that the values of Gmean ± SD will also be shown in this graph using vertical lines.

The following summary statistics will be presented for all the PK parameters except for T_{max}:

- Gmean (calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- CV (calculated as $100\sqrt{[\exp(s^2)-1]}$, where s is the standard deviation of the data on a logarithmic scale)
- Arithmetic mean calculated using untransformed data
- SD calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for the PK parameters $T_{max:}$

- Median
- Minimum

- Maximum
- Number of observations

12.2.2 Safety data

All safety data will be summarized in a descriptive analysis. Baseline will be the last assessment before dose.

All AEs will be summarized by using the preferred term and system organ class of the current MedDRA dictionary for the dosing period. All serious AEs and discontinuations from investigational treatment will be summarized for each dose group using the current MedDRA dictionary, as well as provided individual narratives and/or line listings.

Continuous variables will be summarised for each dose group using the following descriptive statistics:

- Mean
- SD
- Median
- Minimum
- Maximum
- Number of observations

Categorical variables will be summarised for each dose group in frequency tables.

For vital signs, clinical chemistry and haematology, line plots showing the individual absolute values and mean values over time will be made for each dosing period and each dose group. As for the graphs of laboratory items, the reference ranges will be shown in the line plots.

12.2.3 Demographic data

Baseline demographic characteristics will be listed for each subject and summarised **for each dose group** using appropriate summary statistics:

- Mean
- SD

- Median
- Minimum
- Maximum
- Number of observations

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarised by dosing period **for each dose group**.

12.2.4 Exposure

Exposure to investigational product, i.e., total amount of study drug received, will be listed for all subjects.

Total exposure and total time on study (date of last dose minus date of first dose) will be summarised **for each dose group** by the following:

- Mean
- SD
- Median
- Minimum
- Maximum
- Number of observations

12.3 Determination of sample size

No formal sample size calculation was made for this study. A sample size of 10 evaluable volunteers for each dose group is considered sufficient to characterize the pharmacokinetic characteristics and provide safety and tolerability data in healthy volunteers.

12.4 Interim analyses

There will be no formal interim analysis for this study. However, principal investigator and AstraZeneca appropriate personnel will review the safety data after Group I last subject out, to determine if the next sequential cohort (Group II) may be enrolled as planned. The safety data (including all adverse events and laboratory data collected during the Group I drug

administration phase) will be summarized and made available to the ethics committee for endorsement prior to the start of the enrolment of subjects in Group II.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at AstraZeneca Research and Development.

Table 6 Emergency contacts

Name	Role in the study	Address & telephone number

13.2 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and in the Overdose eCRF module.

An overdose without associated symptoms is only reported in the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e., 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 relevant information is provided to the AstraZeneca Patient Safety data entry site.

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

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study the investigational product, ceftaroline, should be discontinued immediately.

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

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** i.e., 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 relevant information is provided to the AstraZeneca Patient Safety data entry site for SAEs **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, see Section 6.3.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. The outcomes of any conception occurring from the date of the first dose until 3 months after the last dose of study treatment must be followed up and documented.

All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

14. LIST OF REFERENCES – NOT APPLICABLE

Clinical Study Protocol: Appendix B

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00005
Appendix Edition Number	1

Appendix B
Additional Safety Information

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

Life threatening

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

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol: Appendix C

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00005
Appendix Edition Number	1

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample

containment standards are encouraged wherever possible when road or rail transportis used.

Clinical Study Protocol: Appendix D

Drug Substance	Ceftaroline fosamil
Study Code	D3720C00005
Appendix Edition Number	1

Appendix D
WHO Risk Categories

Risk group	Shipping Requirement	Pathogen	Risk to individuals	Risk to the community	Examples of Pathogens and their Risk groups
1	Standard Diagnostic (IATA PI650)	A micro-organism that is unlikely to cause human disease.	NONE OR VERY LOW	NONE OR VERY LOW	Most bacteria, fungi and viruses
2	Standard Diagnostic (IATA PI650)	A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spreadof infection is limited.	MODERATE	LOW	Legionella pneumophila E. Coli 0157
3	Standard Diagnostic (IATA PI650)	A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.	HIGH	LOW	HIV Hepatitis B Hepatitis C
4	High risk(IATA PI602)	A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.	HIGH	HIGH	Lassa Fever Ebola Virus

If a subject is being withdrawn due to a suspected infection in WHO risk categories 2, 3 and 4, no biological samples from this subject are allowed to be sent to the laboratory. Samples will be destroyed according to normal routines at the study site.

AstraZeneca

Clinical Study Protocol Appendix E

Drug Substance	Ceftaroline Fosamil
Study Code	D3720C00005
Edition Number	1.0

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